2018 Park City AP Update

Well-differentiated hepatocellular lesions

Evidence-based Immunohistochemical Panels

Sanjay Kakar, MD
University of California, San Francisco

Outline

Hepatocellular adenoma

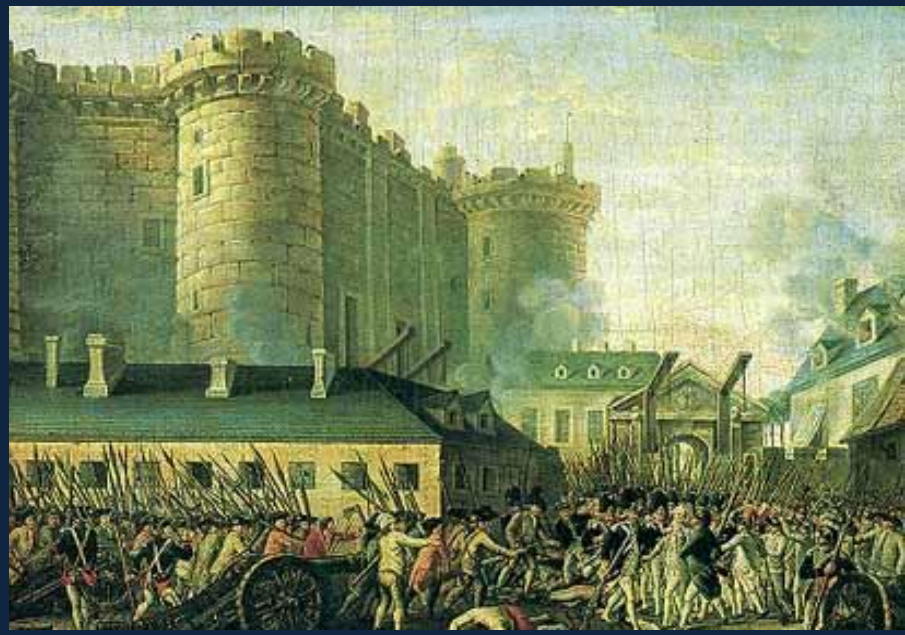
- WHO Classification
- Role of Immunohistochemistry
  - Diagnosis of histologic subtypes
  - Distinction from HCC and FNH

Hepatocellular adenoma

A story of two revolutions

American Revolution

French Revolution



Oral contraceptives and HCA

Janet Baum, MD
Dept of Radiology
Beth Israel, Harvard Univ

Journal reviews

JAMA

New England Journal of Medicine

Radiology

Rejected with ridicule

Lancet. 1973;2:926-9.

Possible association between benign hepatomas and oral contraceptives.

Baum JK, Bookstein JJ, Holtz F, Klein EW.

Abstract

7 case reports of women with benign hepatic adenoma suggest that, since all of the women were taking oral contraceptives (OCs), there may be an association between ingestion of exogenous hormones and development of benign hepatoma of the liver. The cases were rapidly diagnosed by using hepatic arteriography; prompt, precise diagnosis is emphasized because, though the tumors are benign, they may cause serious, if not fatal, hemorrhage if left unchecked. Case 1 was a 26-year-old woman who had taken Enovid for 2 years, who presented with acute abdomen and impending shock. Coliotomy was performed, in which a left-lobe hepatic tumor was found; she underwent left hepatectomy and cholecystectomy and no evidence of recurrence was found 1 year later. Case 2 had been taking Oracon for a unknown time. Case 3, on OCs for 6 years, had a pedunculated mobile tumor removed. Case 4, 25 years old, had been taking Ovral for 6 months before diagnosis and excision of a right lobe liver tumor. Case 5, 5 years on combined OCs, required surgical intervention for a hypervascular mass. Case 6, taking a total of 8 years of OC therapy, was operated on for an hepatic mass which was a white-to-yellow hemorrhagic mass. Case 7, taking Enovid for 7 years, yielded a surgical specimen that was hemorrhagic, partly necrotic, and yellow-tan, about 10 cm in diameter.

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AMERICAN MEDICAL ASSOCIATION

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JOHN D. ARCHER, MD
Senior Editor
(312) 751-6326

February 19, 1975

Janet K. Baum, M.D.
Department of Radiology
University Hospital
University of Michigan
Ann Arbor, Michigan 48104

Re: Ms. #13353, "Liver Tumors and Oral Contraceptives," Baum et al; and
Ms. #13307, "Liver Cell Adenoma and Oral Contraceptives," Antoniades

Dear Doctor Baum:

The Journal will be pleased (even with some embarrassment) to publish your letter in a future issue. Evidently, some editors of The Journal missed the boat about five years ago--but I must admit that any of us may do so sometimes.

I have changed the wording slightly at one point: I do not believe we can confidently say that Dr. Mays made no mention of your article. It is possible that he did so and the Medical News reporter just didn't record the fact.

Hepatocellular adenoma

The French Revolution

HCA: genetic classification

HNF-1α inactivation	*TCF1* gene that encodes hepatocyte nuclear factor
β-catenin activation	*CTTNB1* exon 3 mutation (encodes β-catenin
IL-6 pathway activated (Inflammatory)	*IL6R* gene (encodes gp130), *FRK*, *STAT3*, *GNAS*
Mutation-negative	No *HNF-1α* or β-catenin mutation

Zucman-Rossi, Hepatology, 2006
WHO blue book, 2010

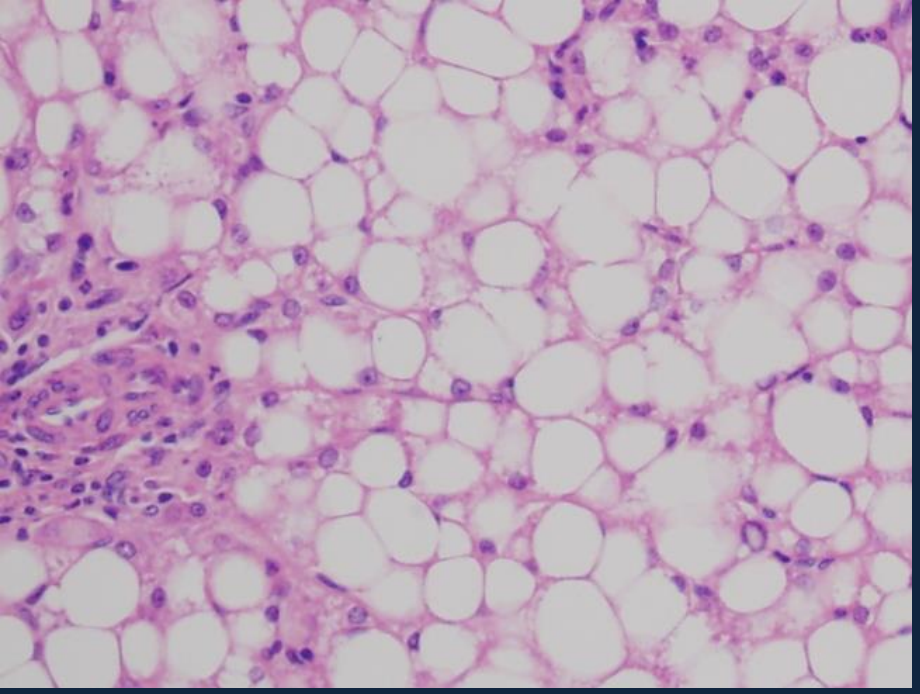
HCA subtypes

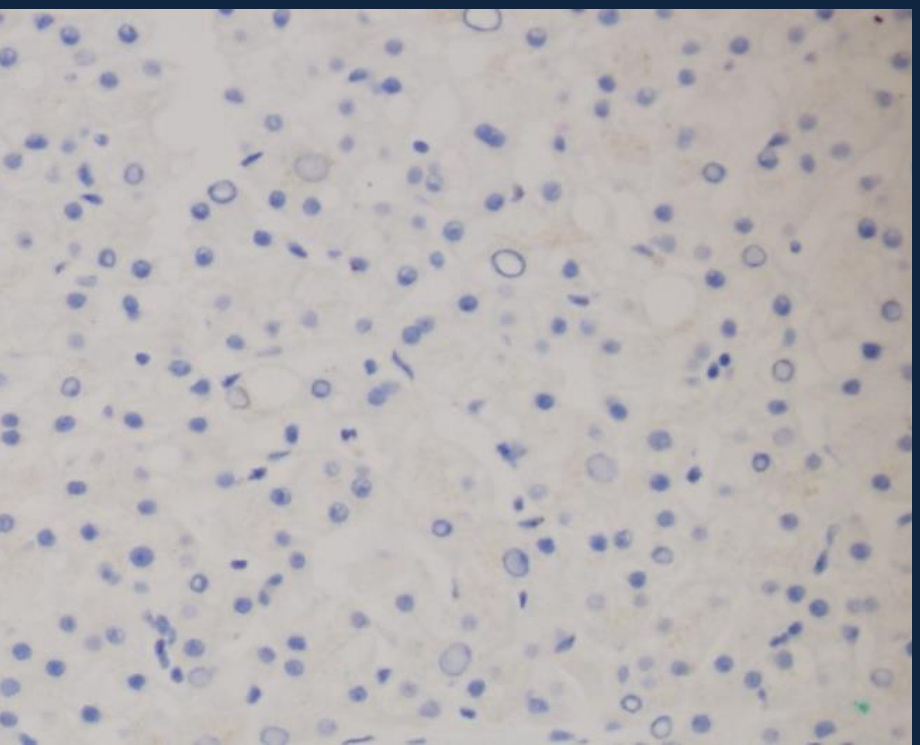
	HNF1α-mutated	β-catenin mutated	Inflammatory
Women	~90%	~ 60%	~90%
Histologic features	Steatosis	Cytologic abnormalities	Sinusoidal dilatation Inflammation Ductular reaction
Association with HCC	Rare	40%	Uncommon

HCA: immunohistochemistry

HNF-1α mutated	β-catenin mutated	Inflammatory	Unclassified
-Liver fatty acid binding protein (LFABP)	-β-catenin -Glutamine synthetase (GS)	-C reactive protein (CRP) -Serum amyloid associated protein (SAA)	No defining features
LFABP negative	Nuclear β-catenin Diffuse GS	CRP+ SAA+	

Bioulac-Sage, Hepatology 2007

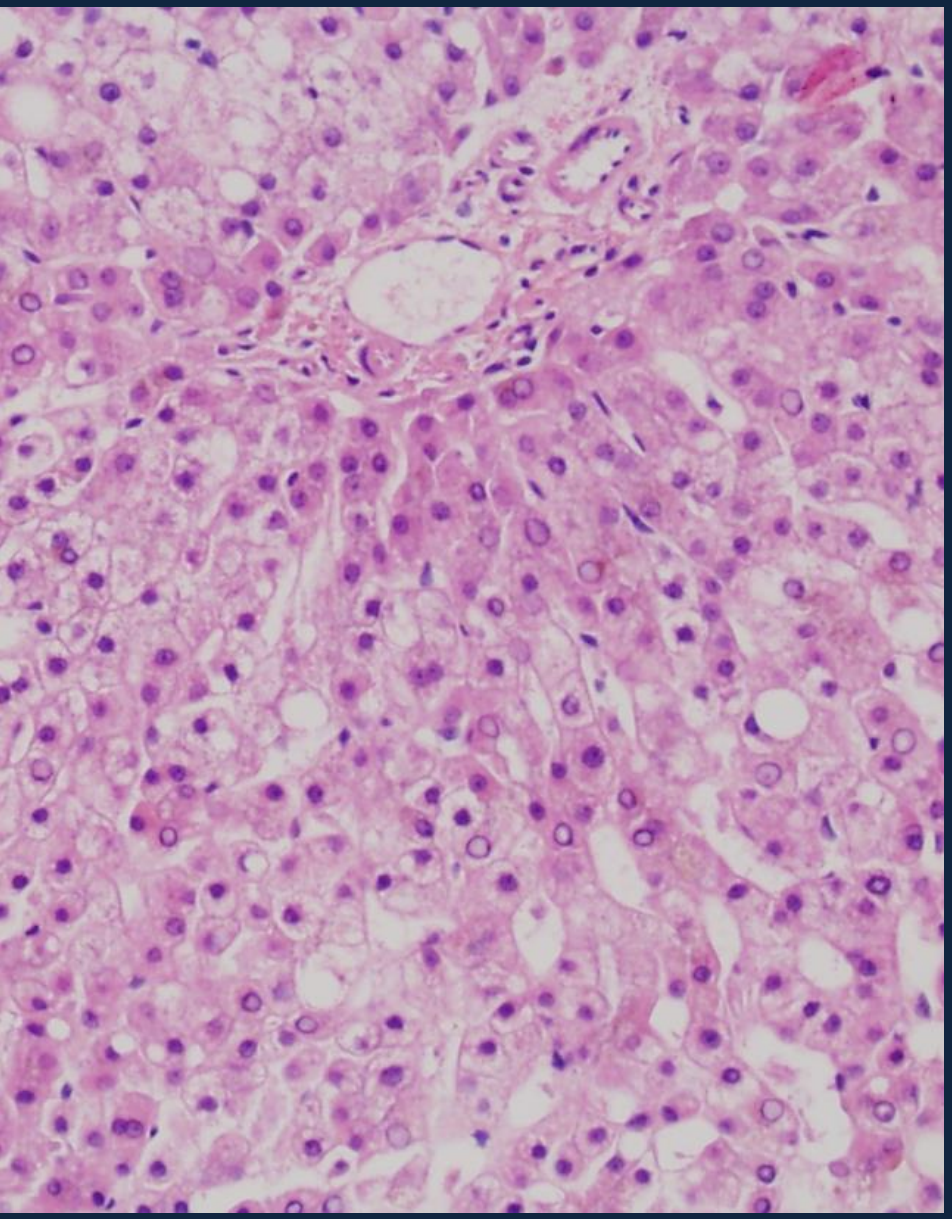


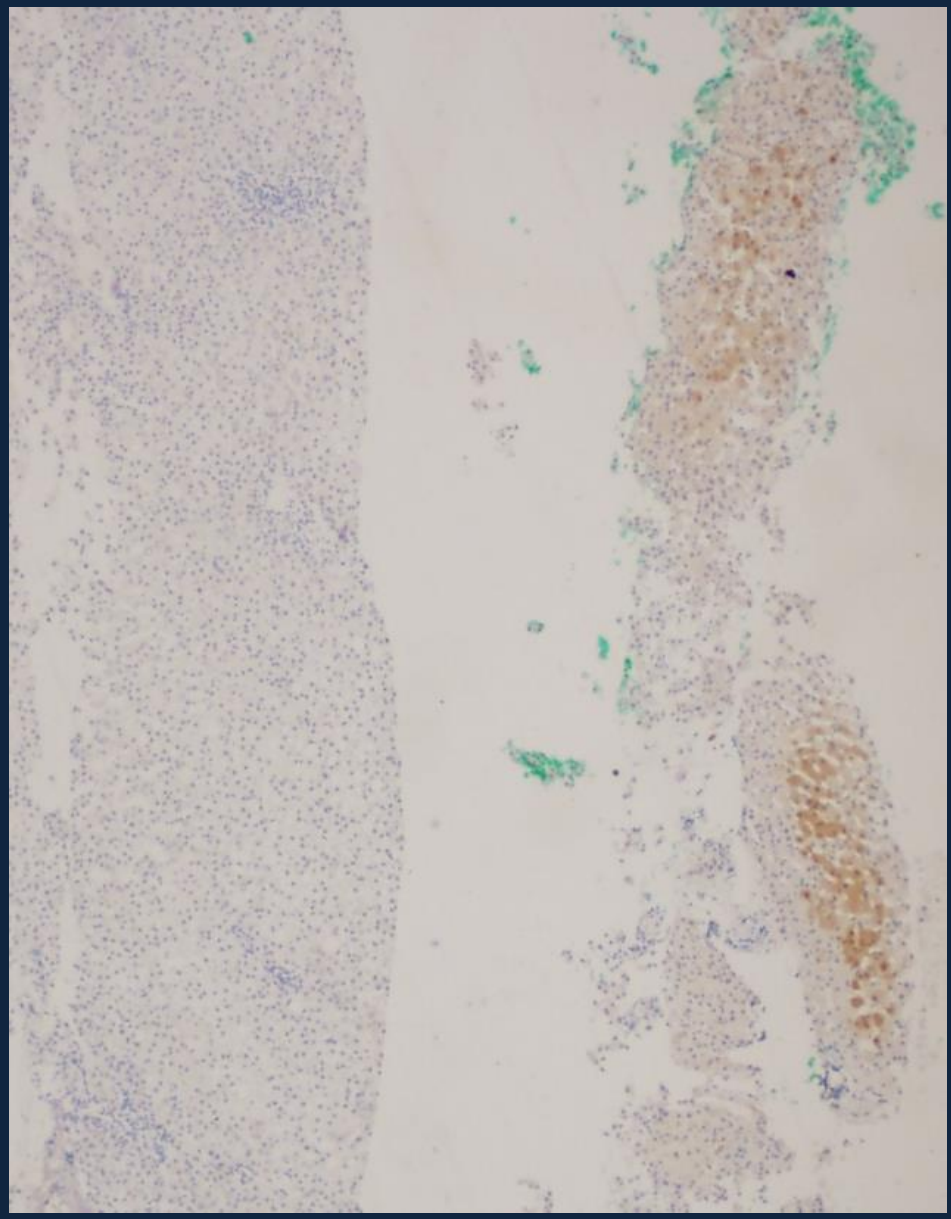


HNF1α mutated (H-HCA)

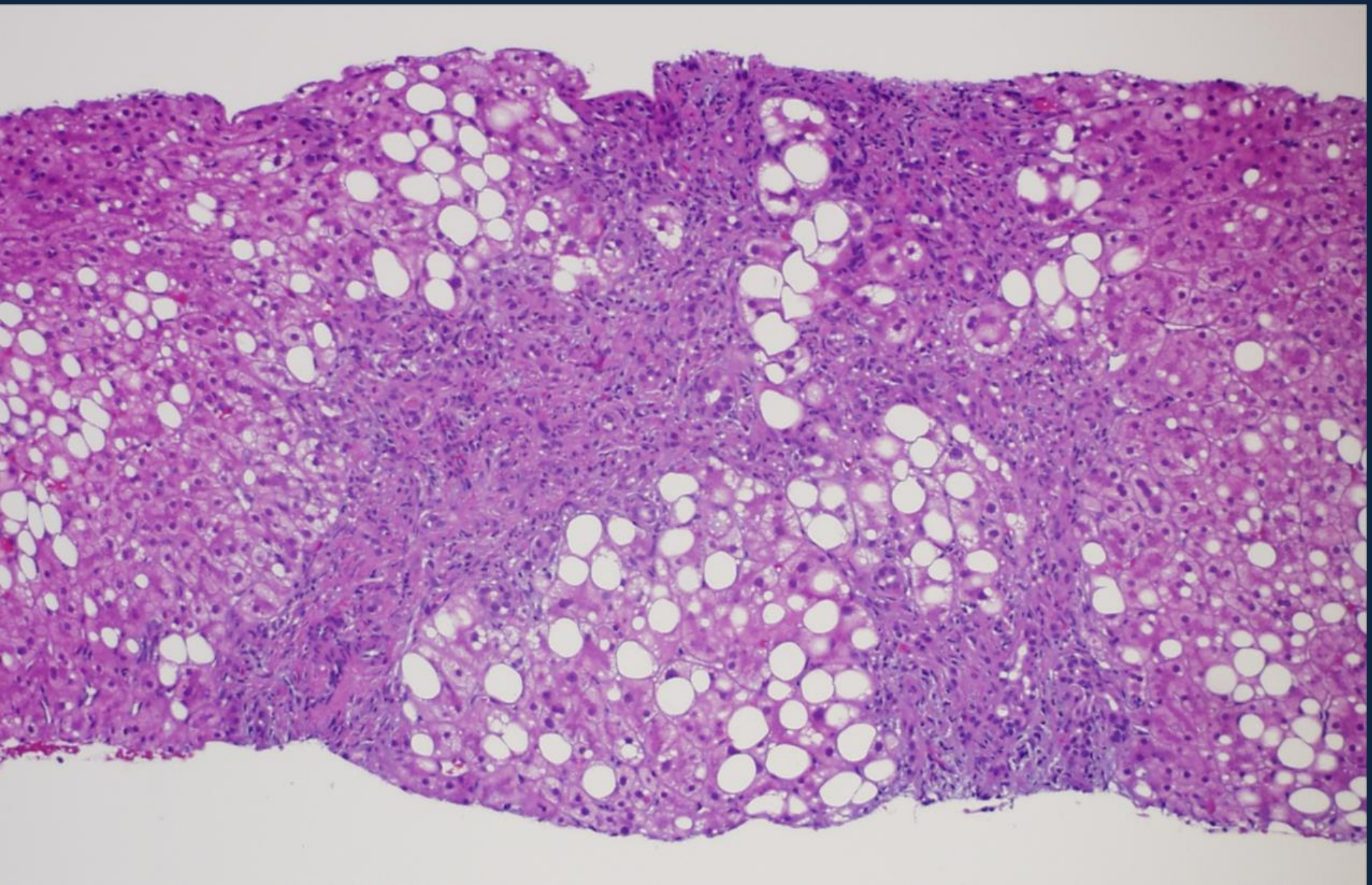
- Women
- Steatosis
- Atypia, risk of HCC: minimal
- Fatty acid binding protein absent

H-HCA without fat





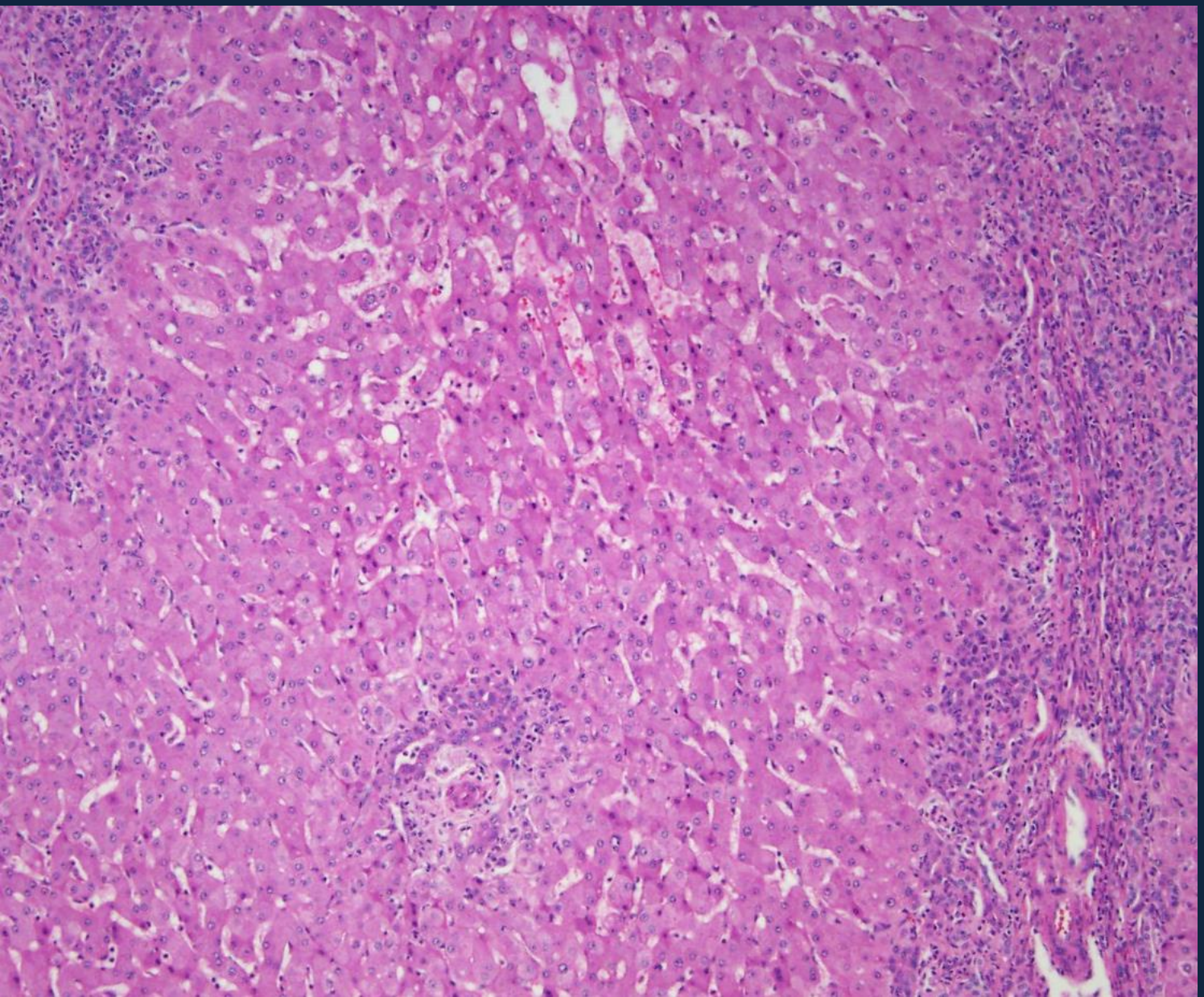
FNH with fat



HCA: genotype-phenotype

HNF1-mutated	Beta-catenin mutated (exon 3)	Inflammatory
-Fatty acid binding protein (FABP)	-Beta-catenin -Glutamine synthetase (GS)	-C reactive protein (CRP) -Serum amyloid associated protein (SAA)
FABP negative	Nuclear beta-catenin Diffuse GS	CRP+ SAA+

Inflammatory hepatocellular adenoma (I-HCA)

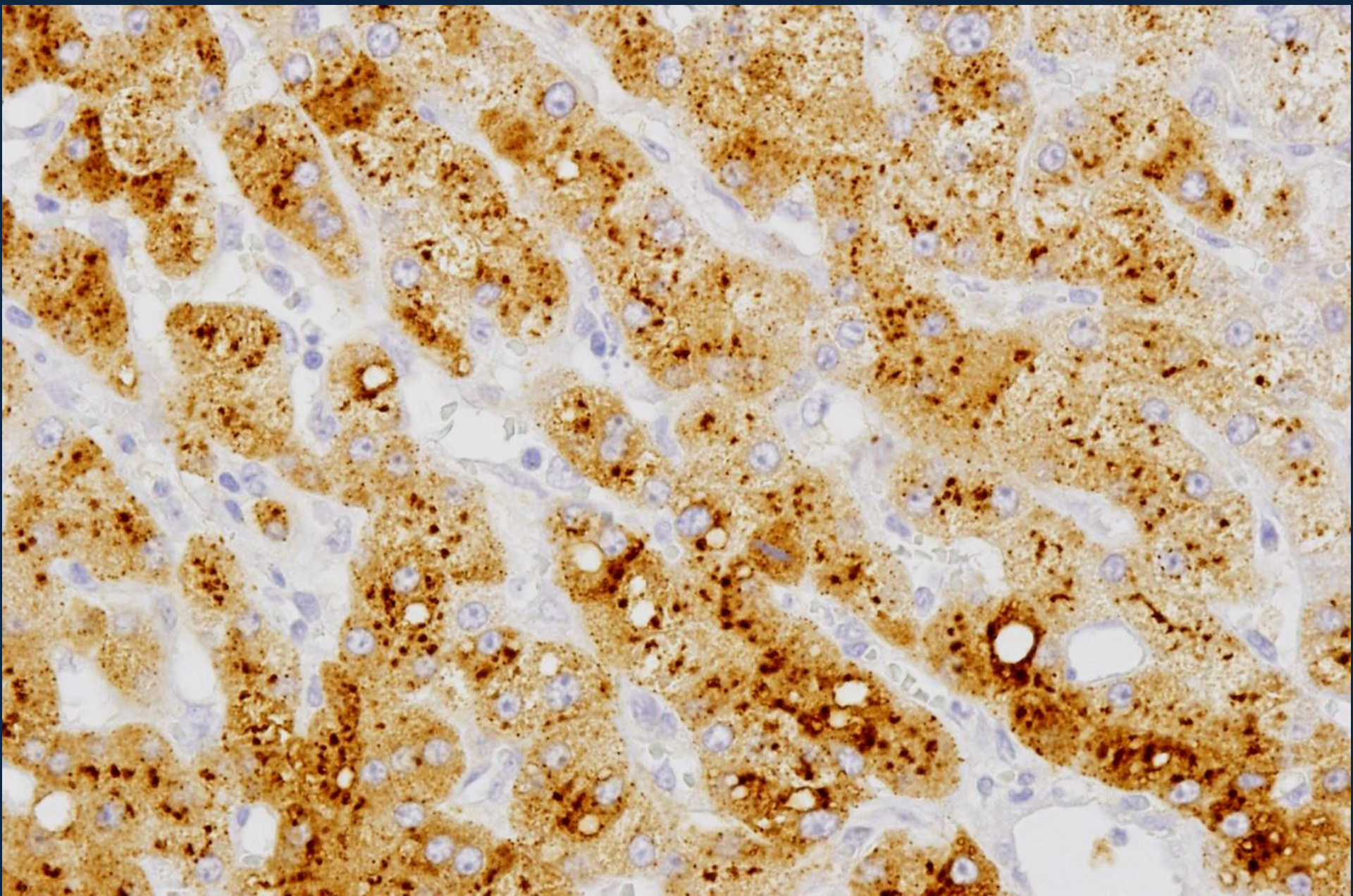


-Inflammation

-Sinusoidal dilatation

-Ductular reaction

SAA in inflammatory adenoma



HCA: immunohistochemistry

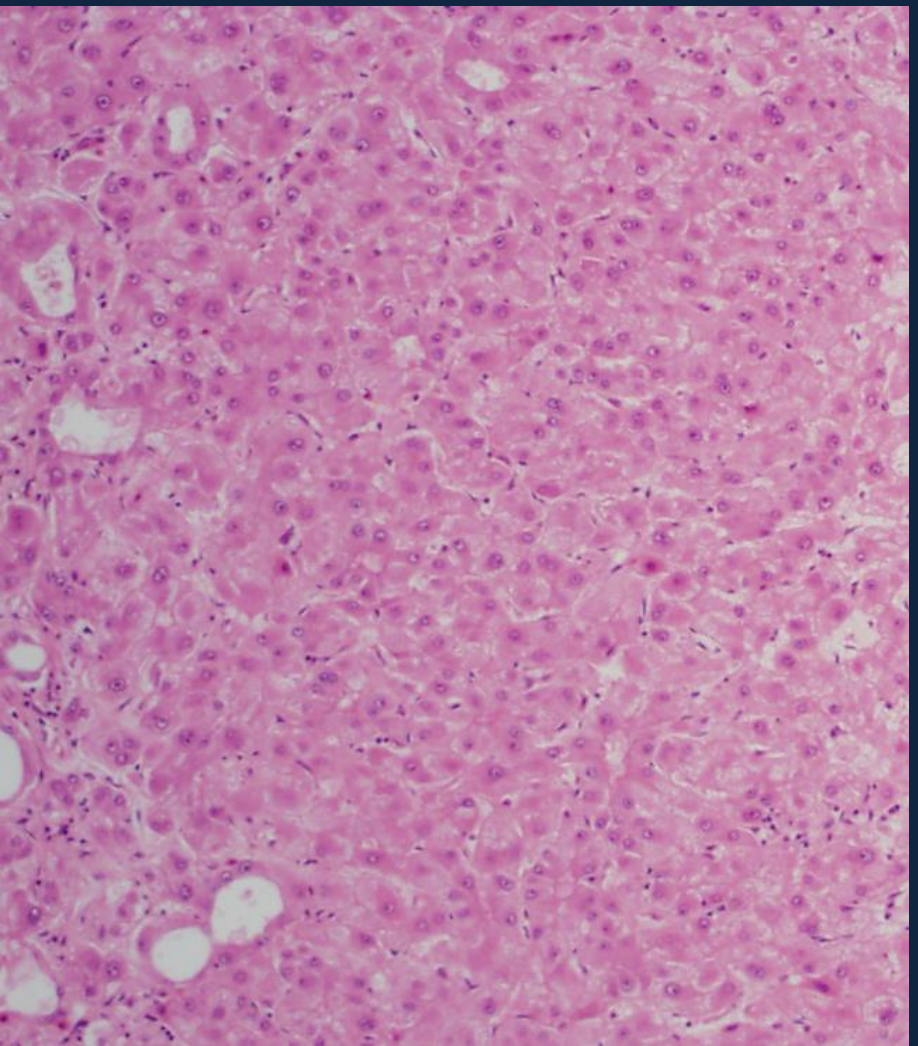
HNF-1α mutated	β-catenin mutated	Inflammatory	Unclassified
-Fatty acid binding protein (FABP)	β-catenin Glutamine synthetase (GS)	-C reactive protein (CRP) -Serum amyloid associated protein (SAA)	No defining features
FABP negative	Nuclear β-catenin Diffuse GS	CRP+ SAA+	

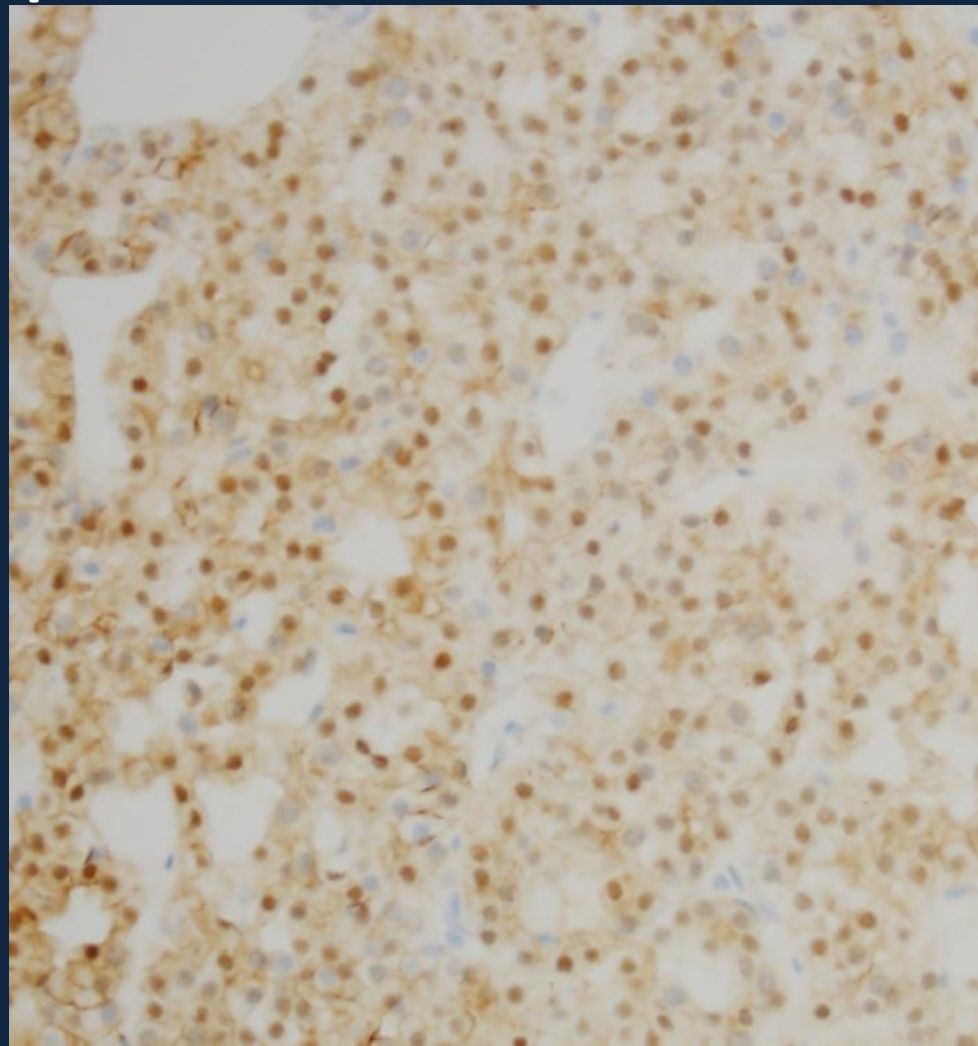
β-catenin mutated, exon 3 (b-HCA)

-40% men

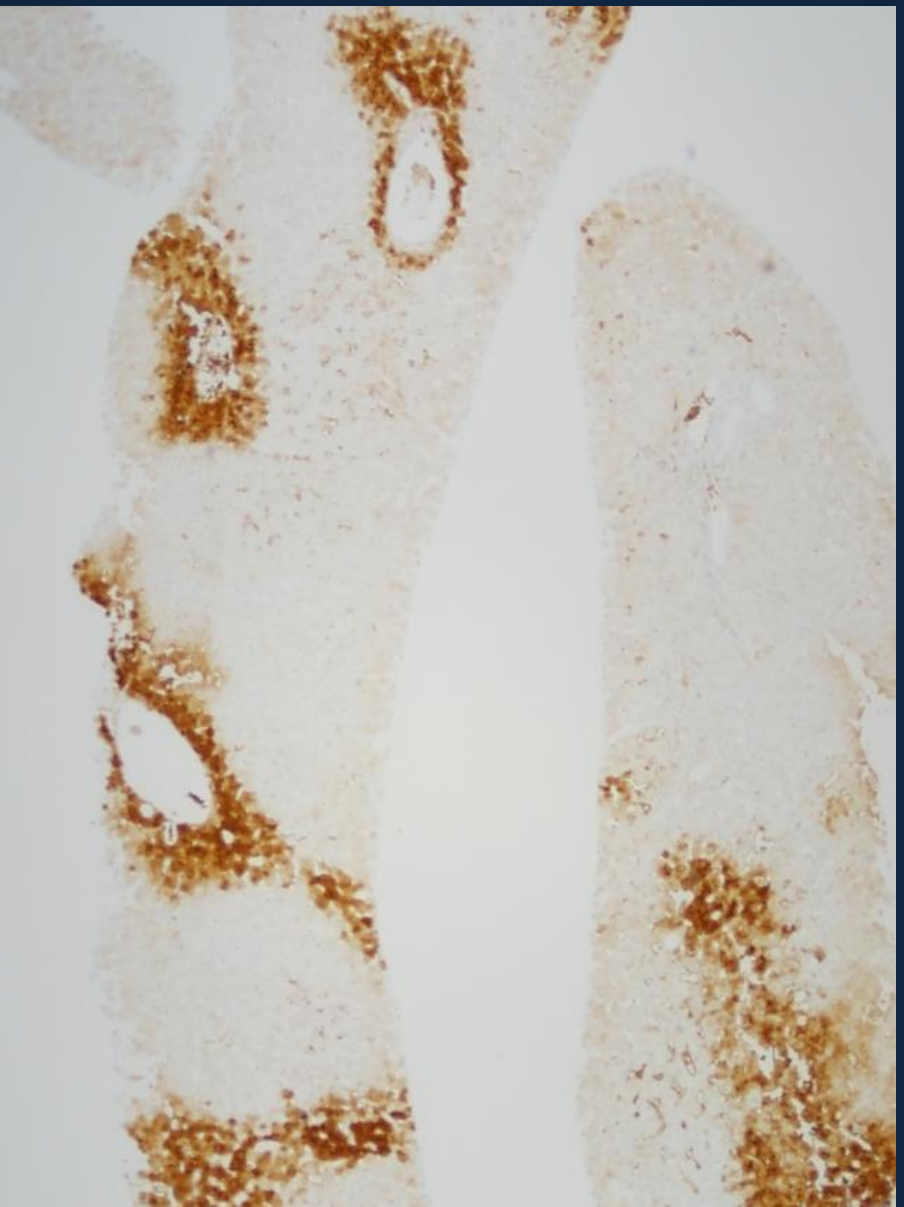
-Cytologic atypia, frequent association with HCC

-Nuclear translocation of β-catenin

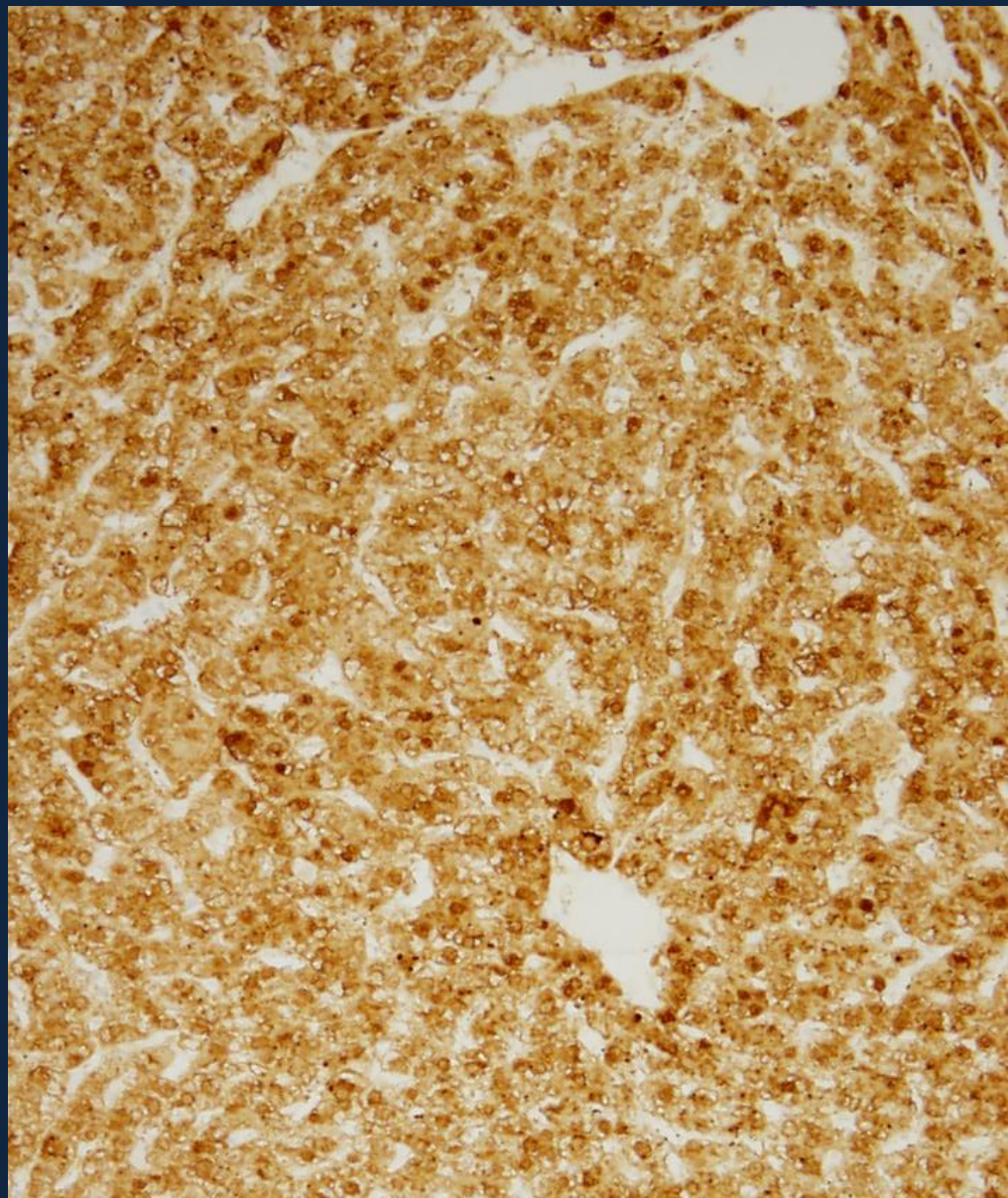




Normal liver: perivenular GS



β-catenin-activation: diffuse GS



HCA: WHO classification 2010

HNF-1α inactivated	Inflammatory	β-catenin activated
35-50%	40-50%	10%
Women, OC use	Women (OCs), men Obesity, diabetes	40% in men Androgens, glycogen storage disease
Marked steatosis, no atypia	Inflammation, sinusoidal dilatation, ductular reaction	Pseudoacinar, small cell change
HCC rare	HCC rare	HCC 40%
LFABP negative	SAA positive CRP positive	Nuclear β-catenin Diffuse GS

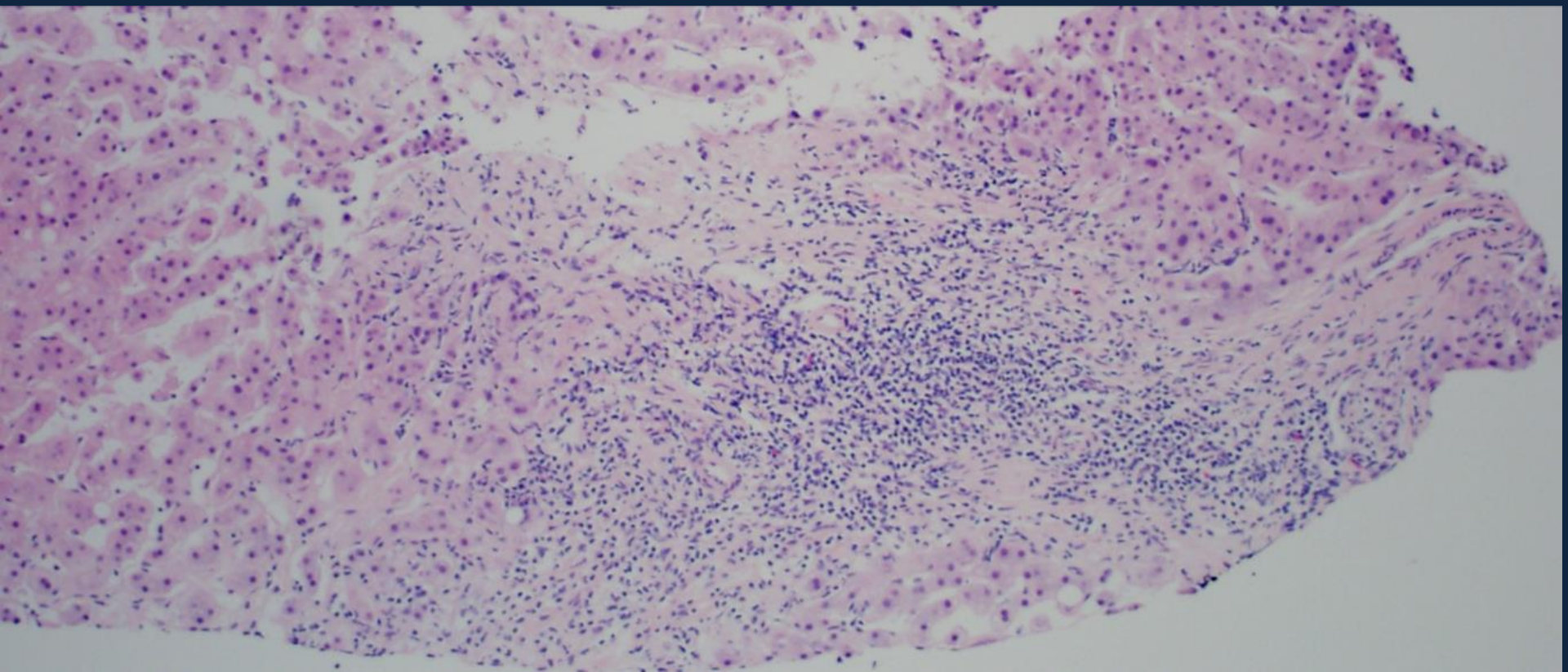
Unclassified (5-10%): no known defining features

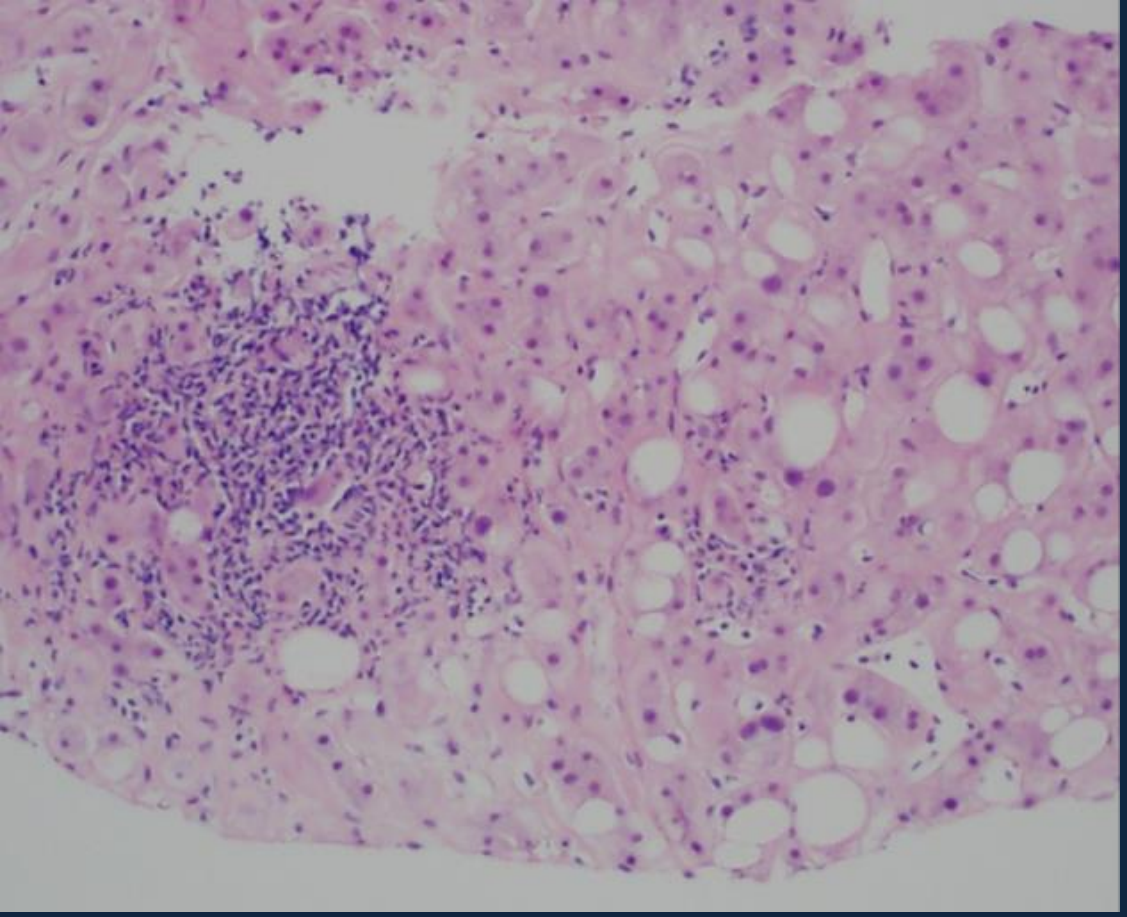
Practical considerations

- Are all stains necessary for clinical care?
- Is it necessary to determine subtype of HCA?
- What is the significance of β-catenin activation

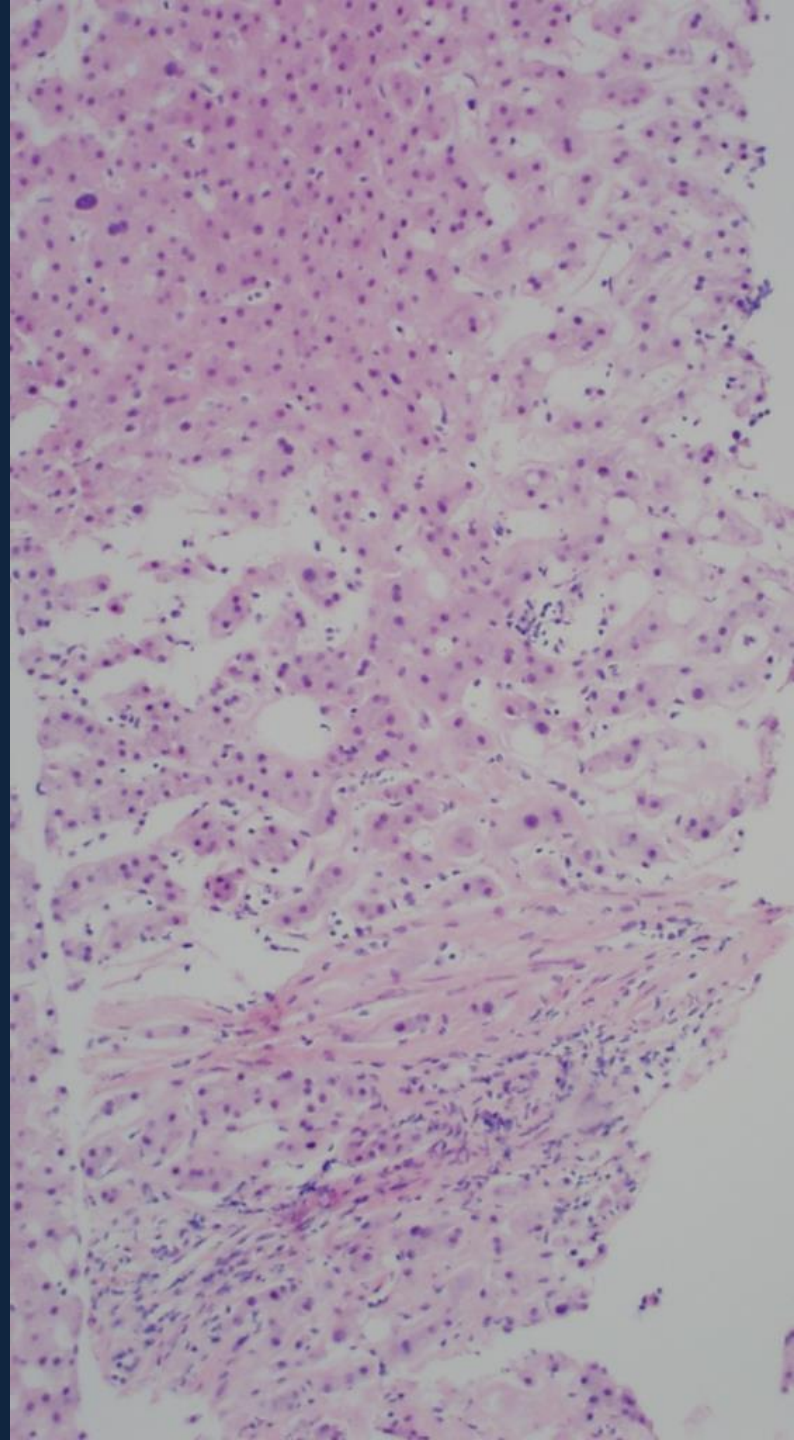
Case 1

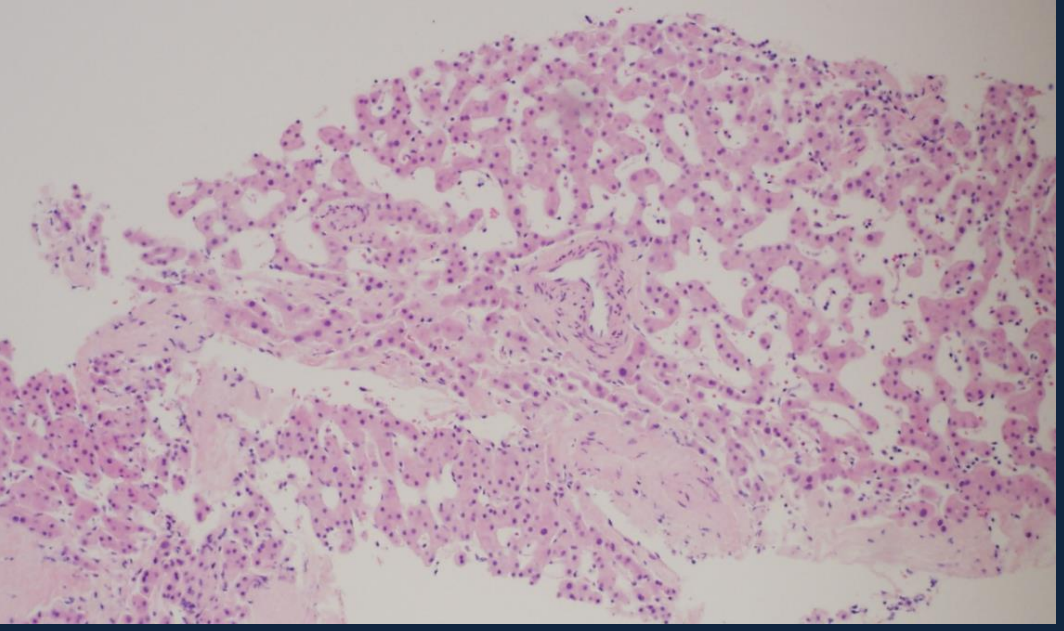
- 32 year old woman on OCs
- Ultrasound for workup of abdominal pain
- 5 cm liver mass, suggestive of FNH on imaging

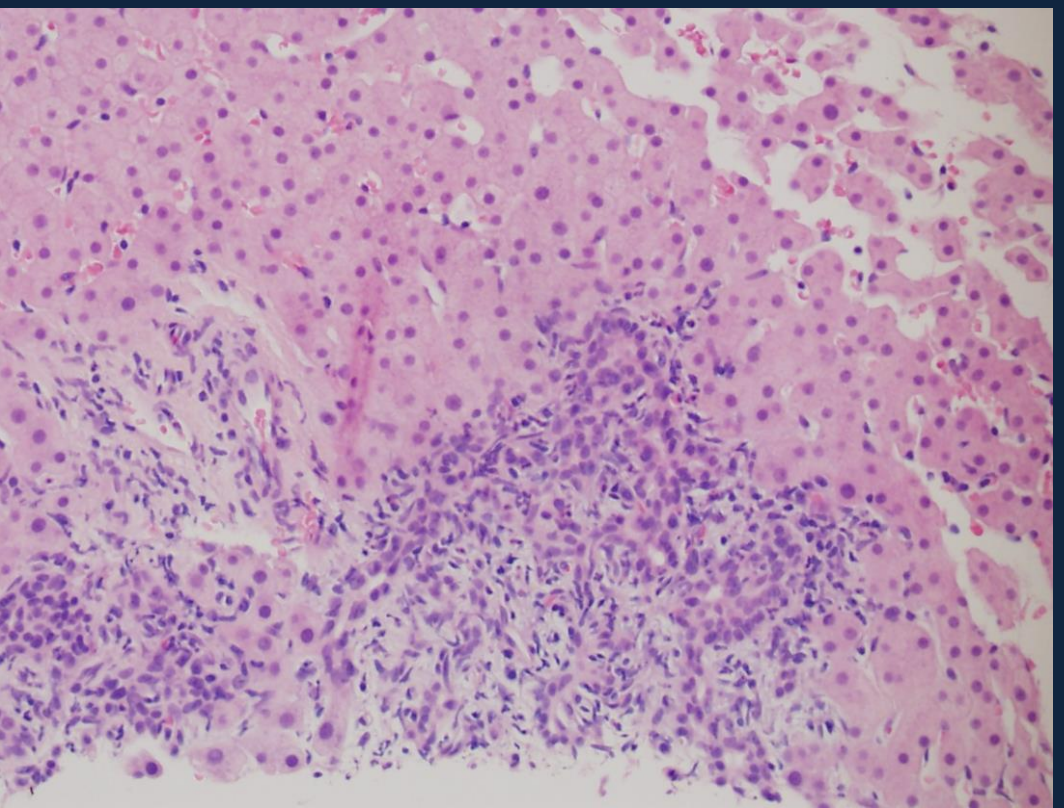


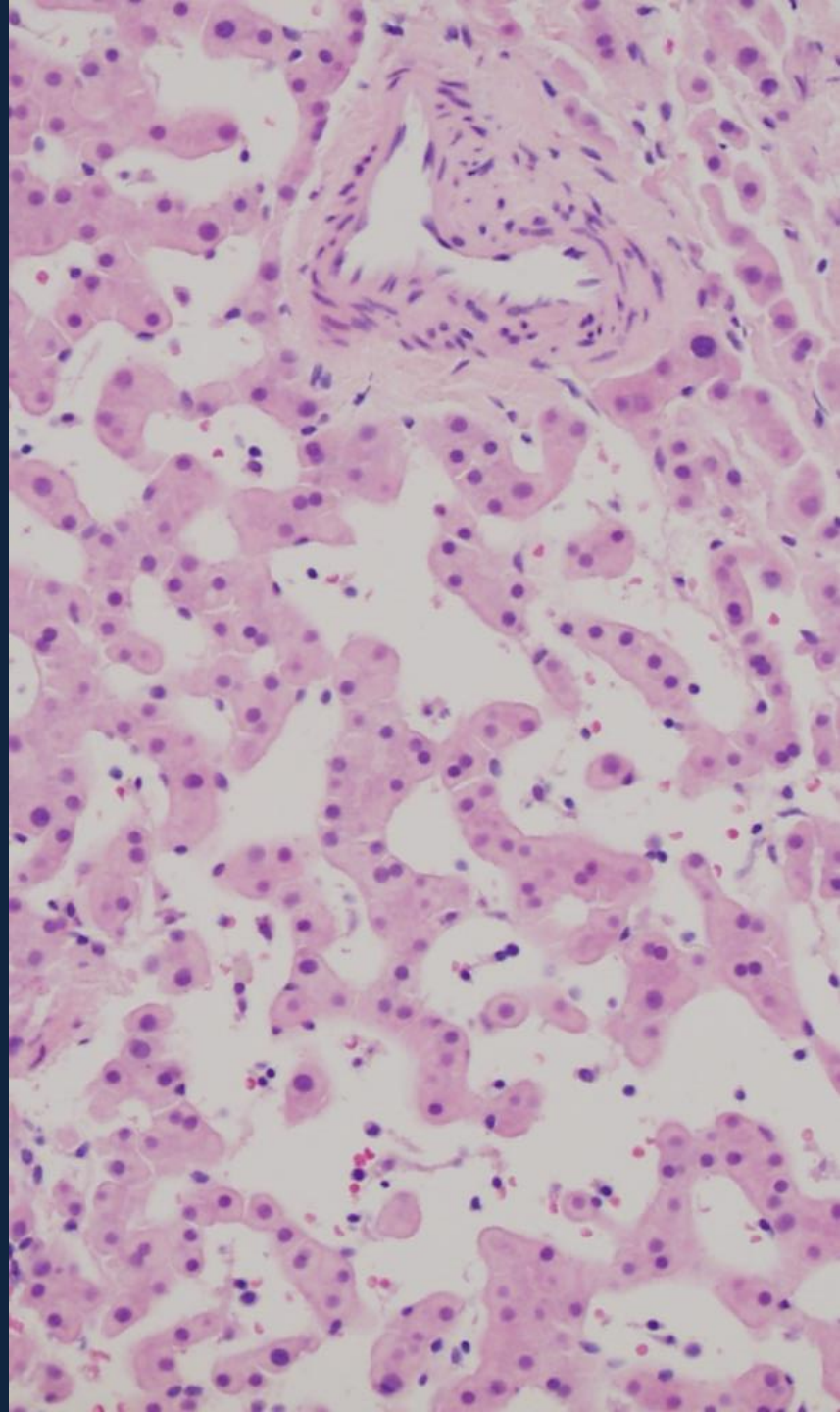


-Inflammation
-Arterioles
-Few ductules
-Sinusoidal dilatation









FNH vs. HCA

	Focal nodular hyperplasia	Hepatocellular adenoma
Clonality	Polyclonal	Monoclonal
Resection	Not required except when symptomatic	Most cases (>5 cm, male gender)

FNH vs. HCA

	Focal nodular hyperplasia	Hepatocellular adenoma
Central scar	Present	Absent
Fibrous septa	Typically present	Typically absent
Nodular architecture	Present	Absent
Ductular reaction	Generally prominent	Absent

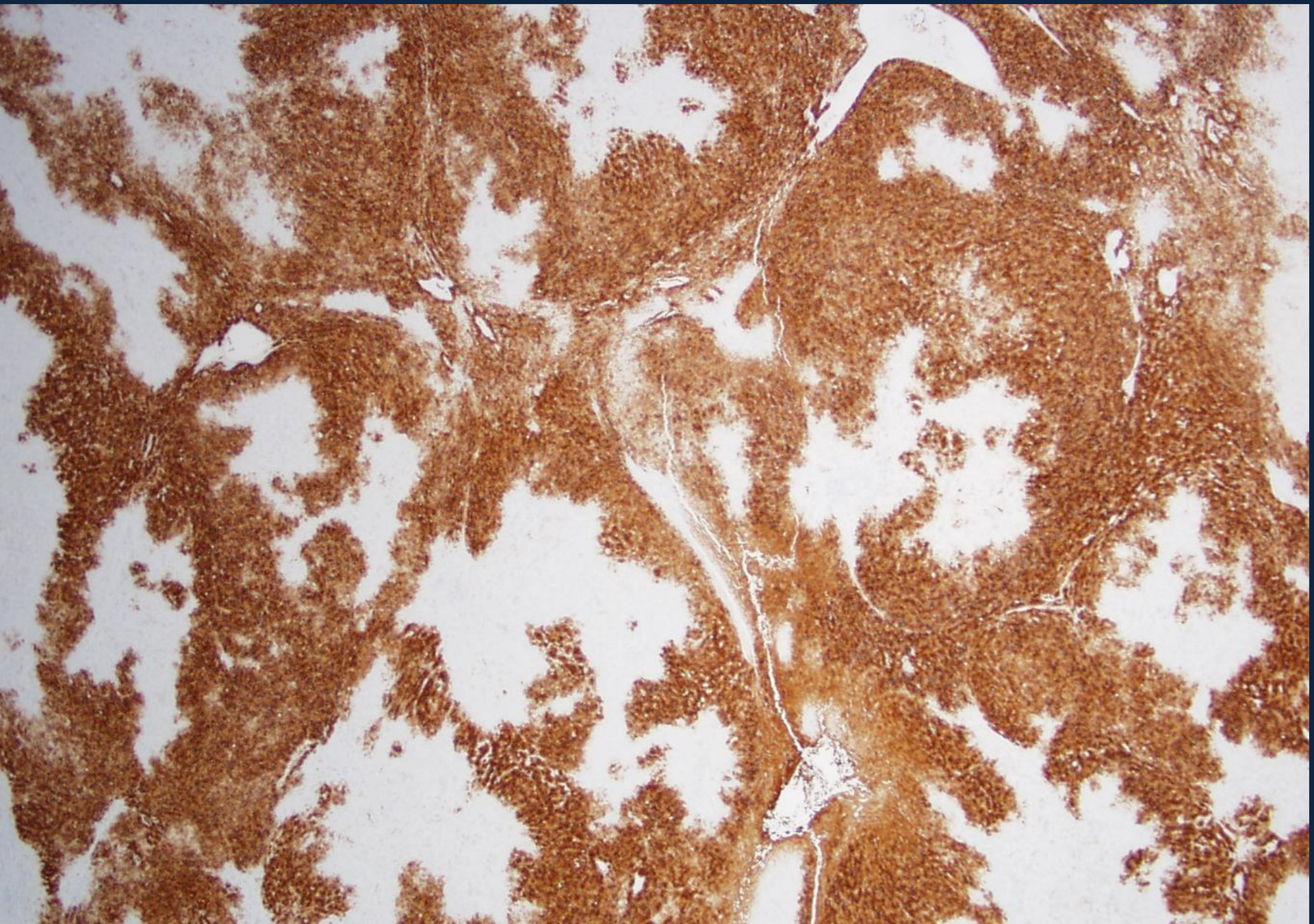
Histologic feature	FNH	Inflammatory HCA
Fibrous bands	90%	26%
Ductular reaction	83%	43%
Sinusoidal dilatation	18%	83%
Inflammation	40%	60%
Steatosis	21%	57%

Joseph/Kakar, Mod Pathol 2014

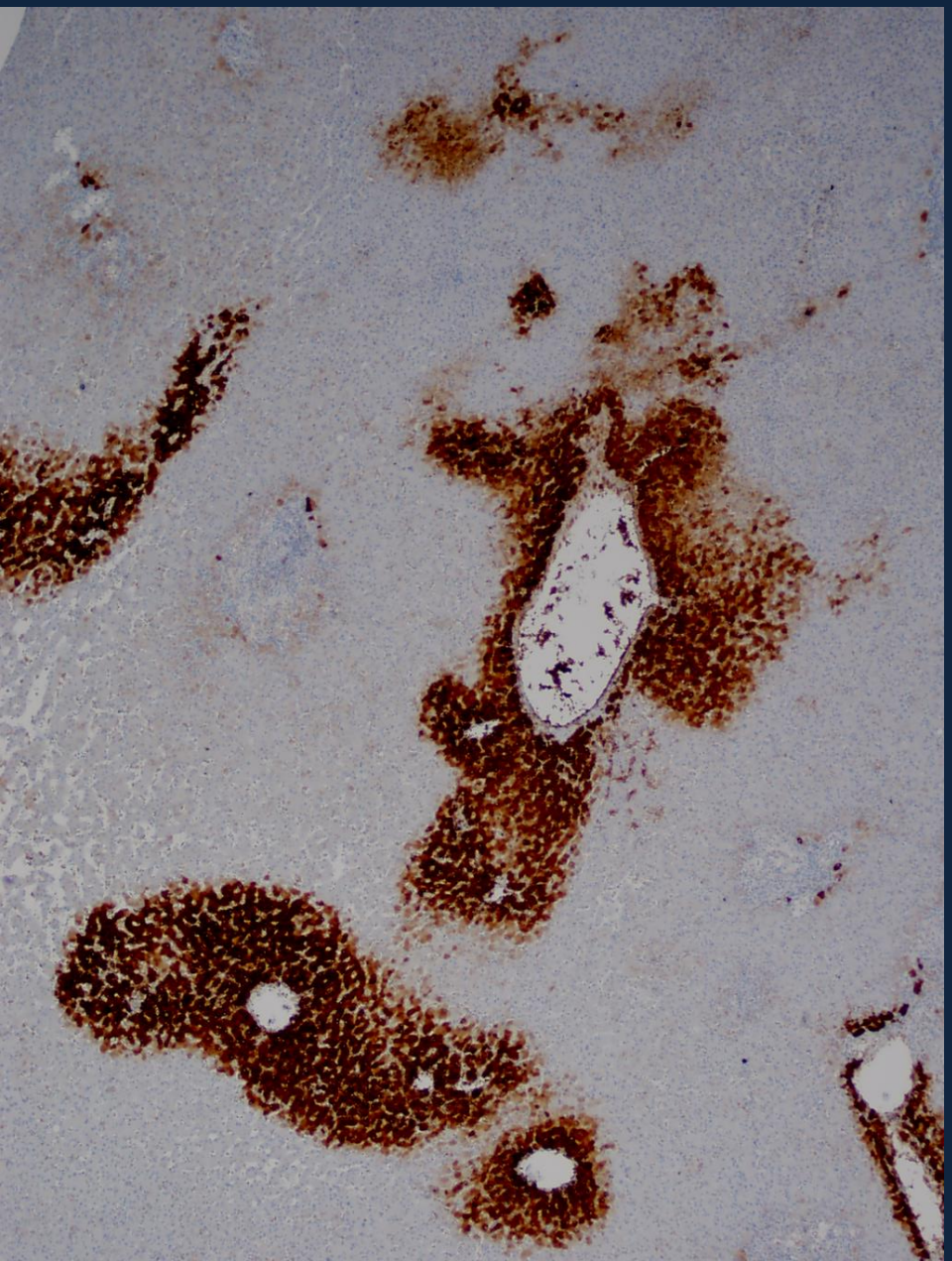
FNH or inflammatory HCA

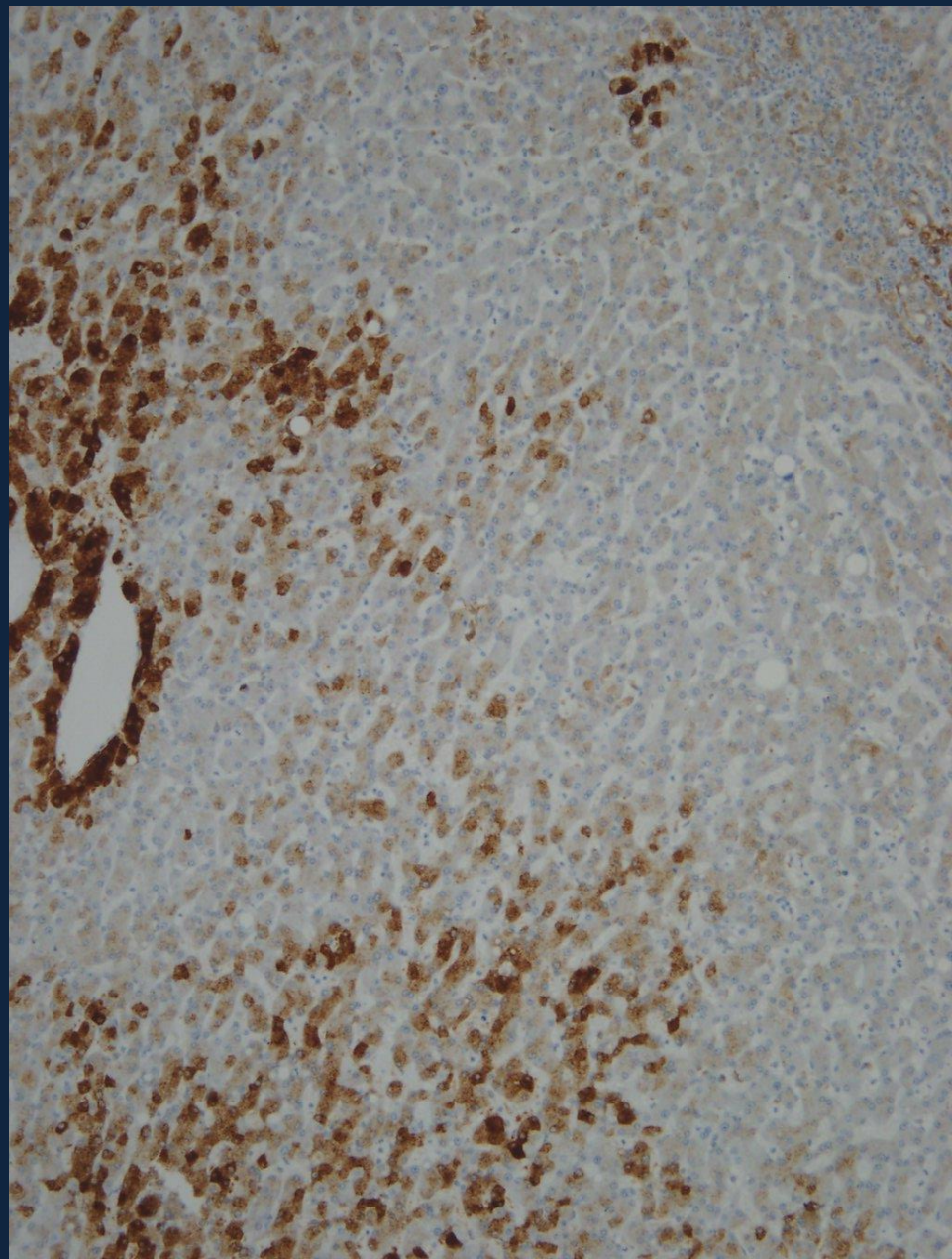
Immunostain	Inflammatory HCA	FNH
Serum amyloid A (SAA)	Moderate to strong	Absent/focal
Glutamine synthetase (GS)	β-catenin activated: diffuse Others: Perivascular/patchy	Map-like

GS: map-like pattern, typical of FNH



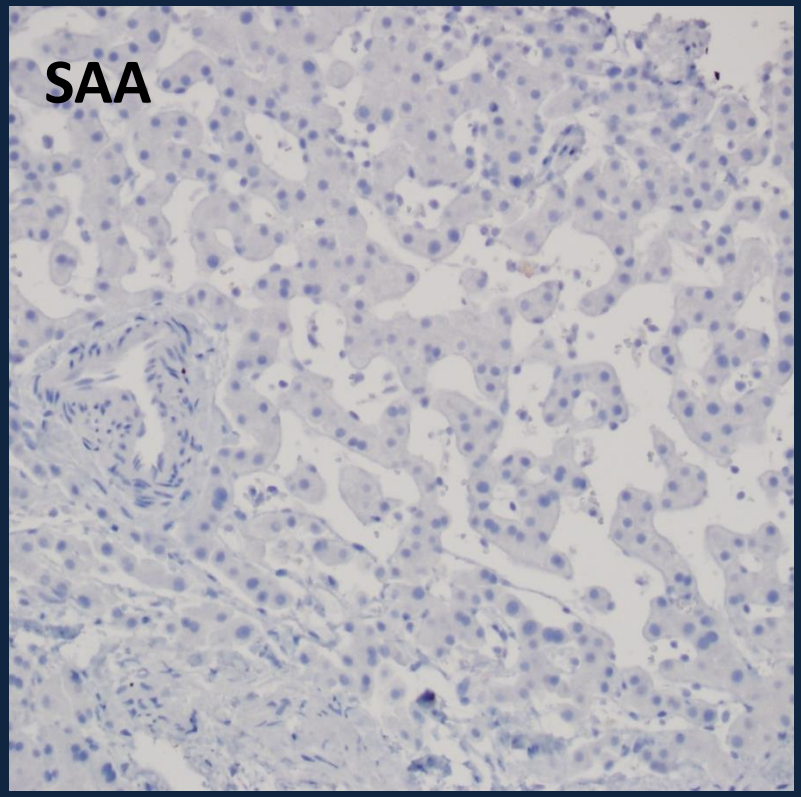
GS: patchy staining ± perivascular staining
Most HCA (without β-catenin activation)



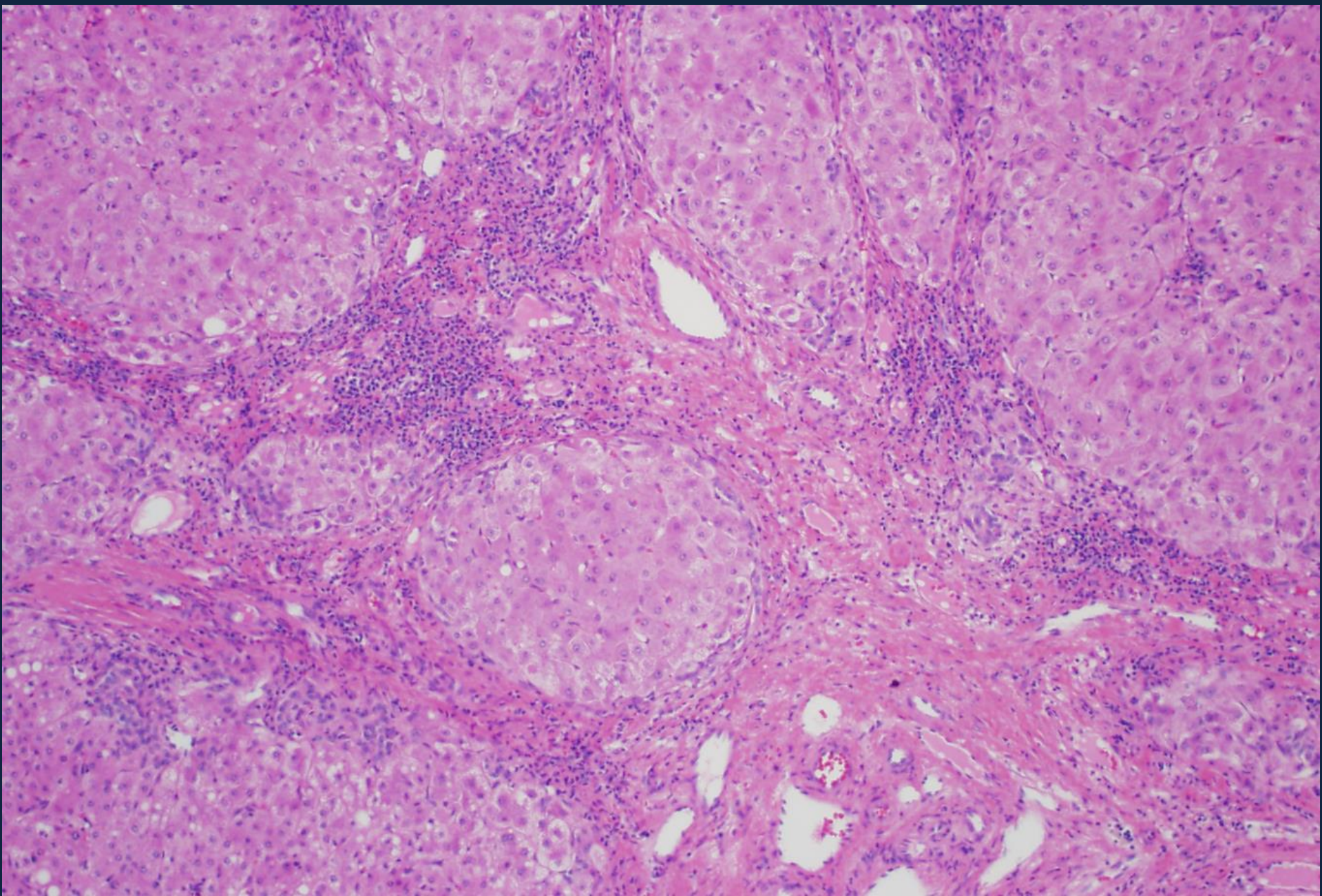


Case 1: FNH with telangiectasia

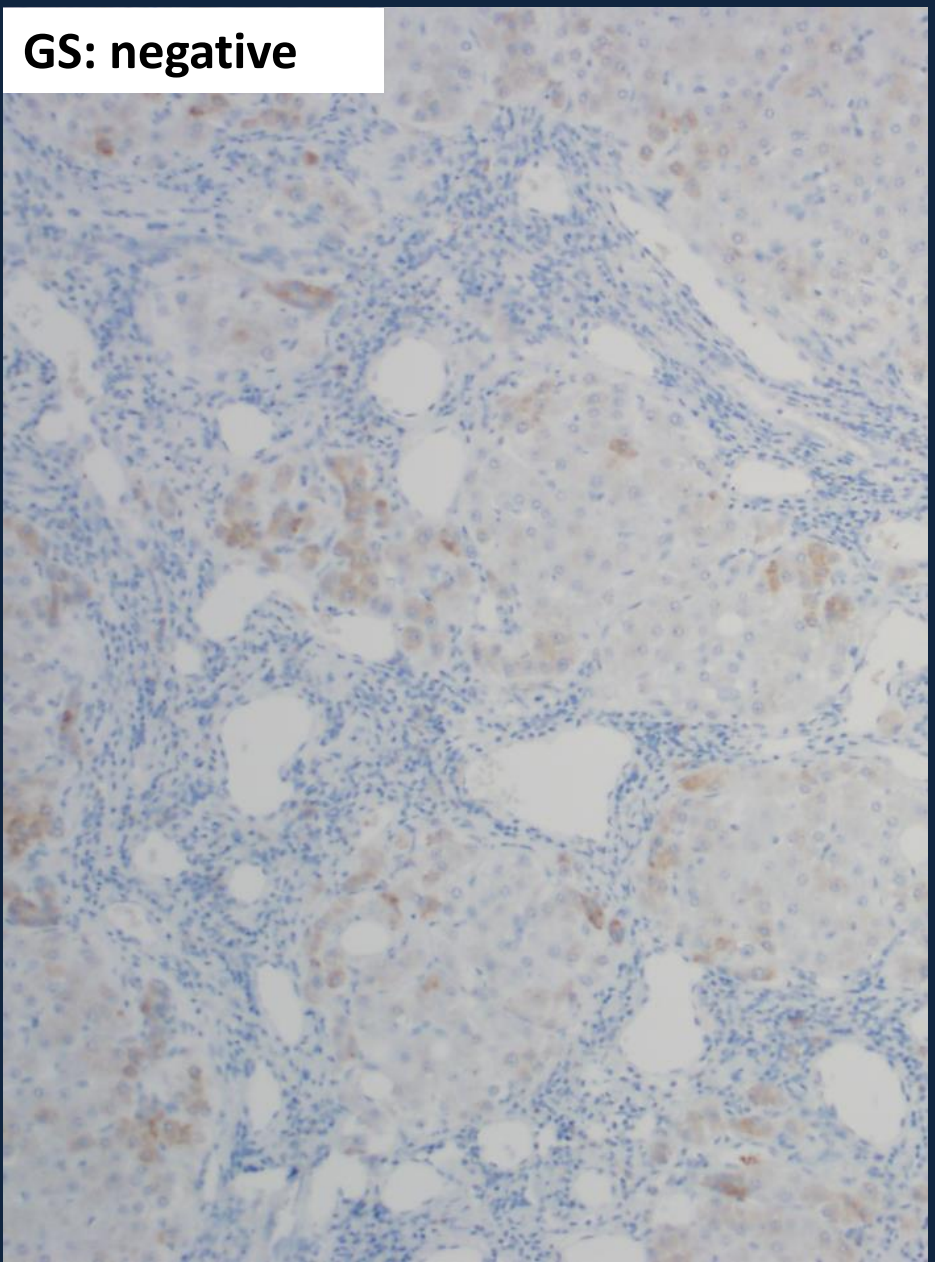
- Map-like GS pattern
- SAA negative

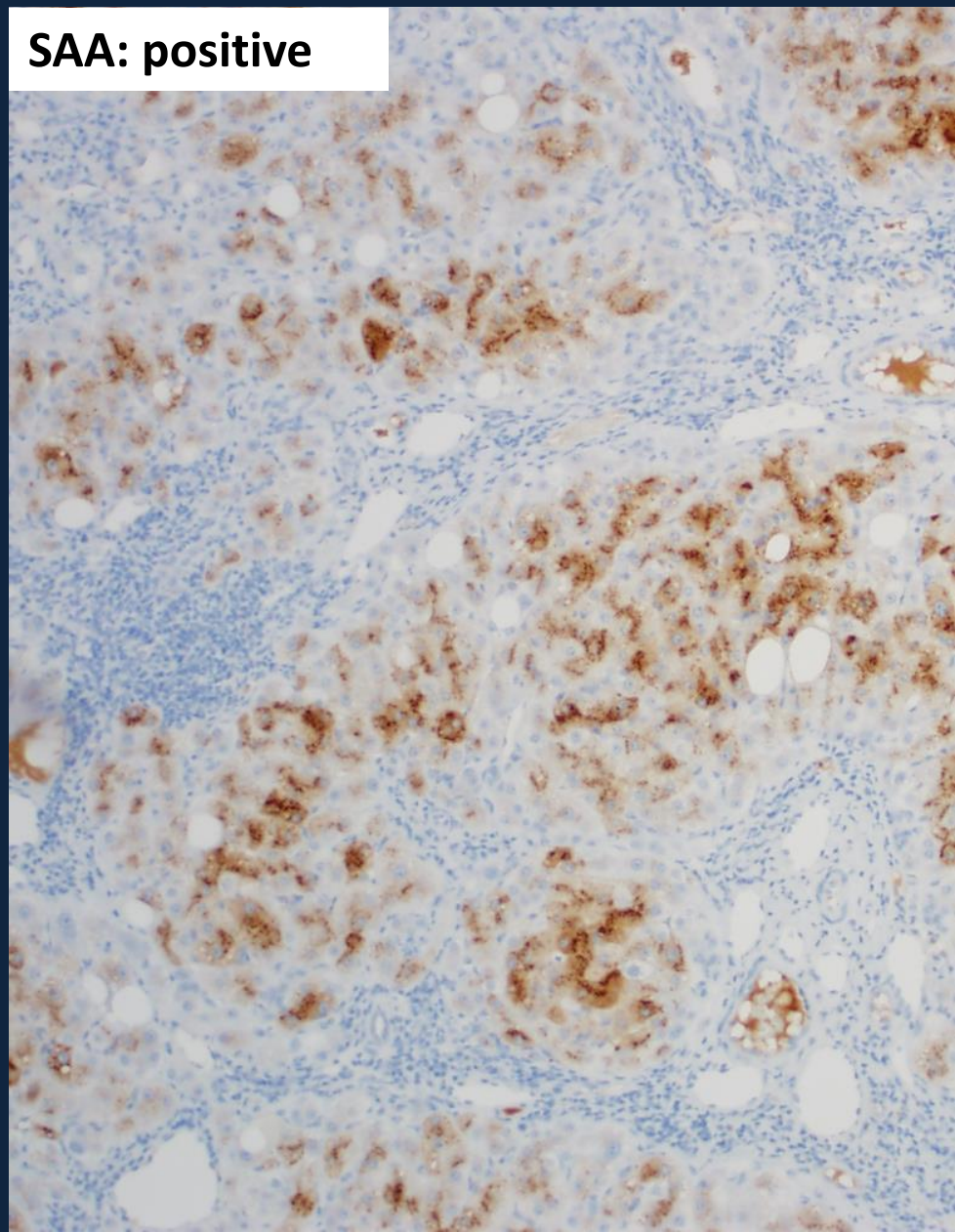


Case 2: 40/F, biopsy from a 4 cm liver mass



Inflammatory HCA





Two stain approach: FNH vs I-HCA

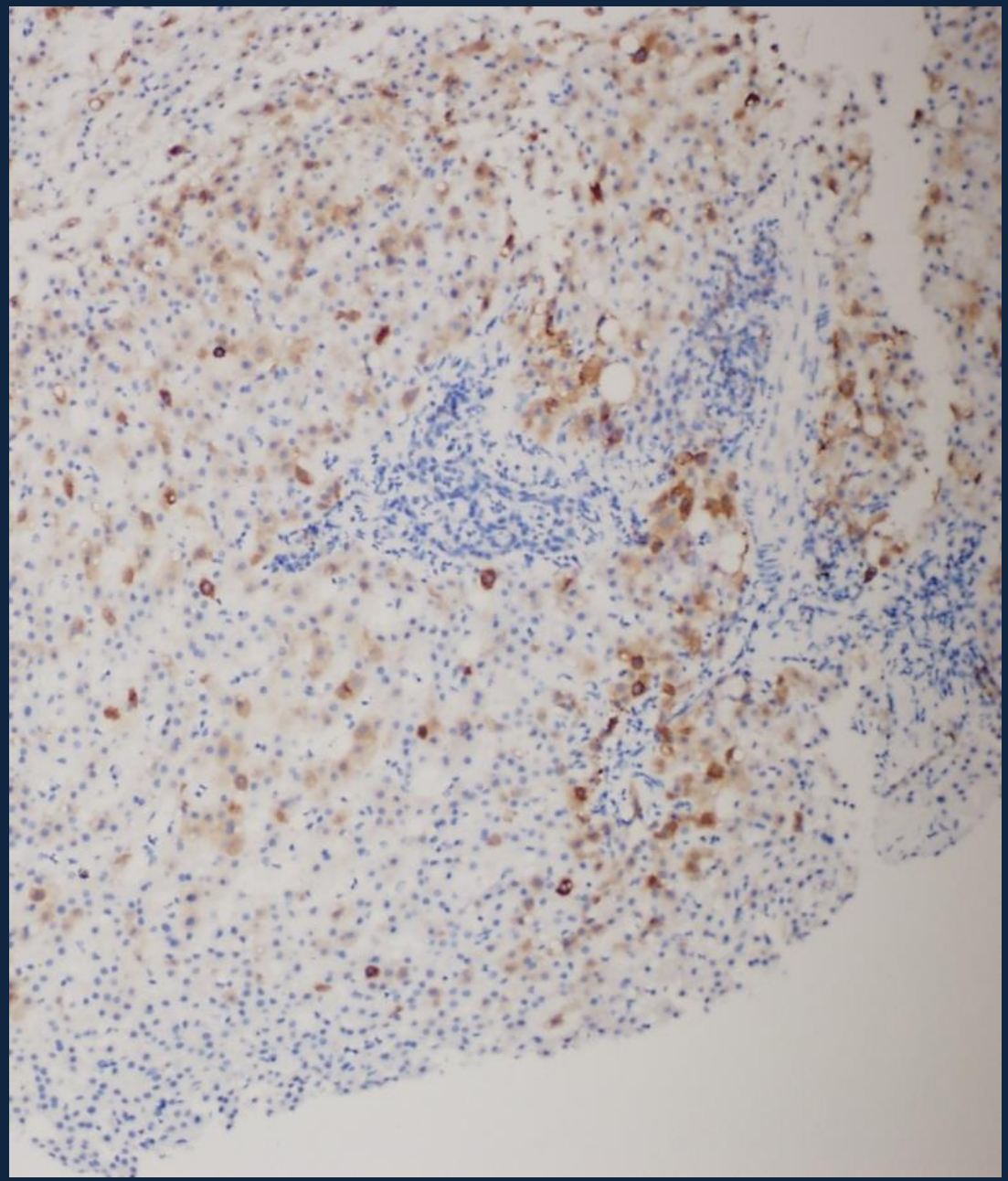
Stain	Interpretation
GS	**Map-like: FNH** ***Irrespective of SAA/CRP***
SAA	**Positive: I-HCA**
CRP	***Diffuse positive: I-HCA***

Indeterminate:

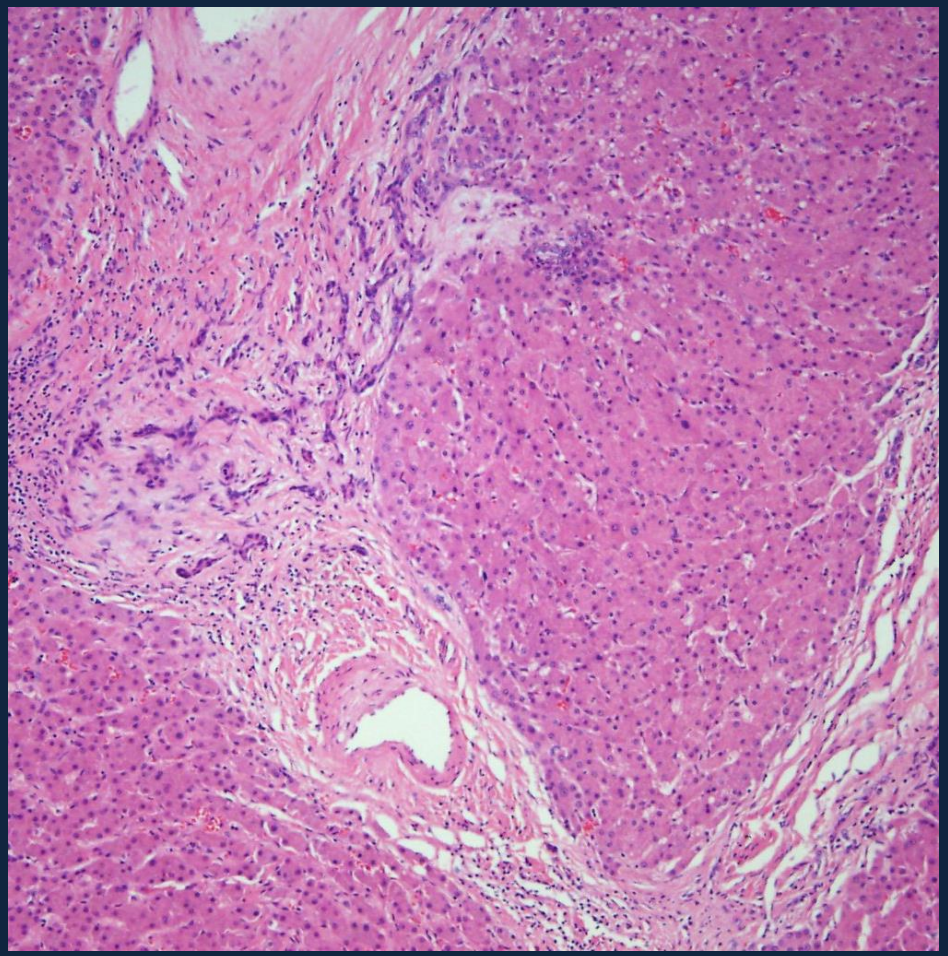
- **Atypical staining patterns, limited biopsy**
- **Further management: follow-up vs. repeat bx**
  - **Morphologic suspicion, additional stains**
  - **Imaging, clinical setting (size, patient age)**

FNH

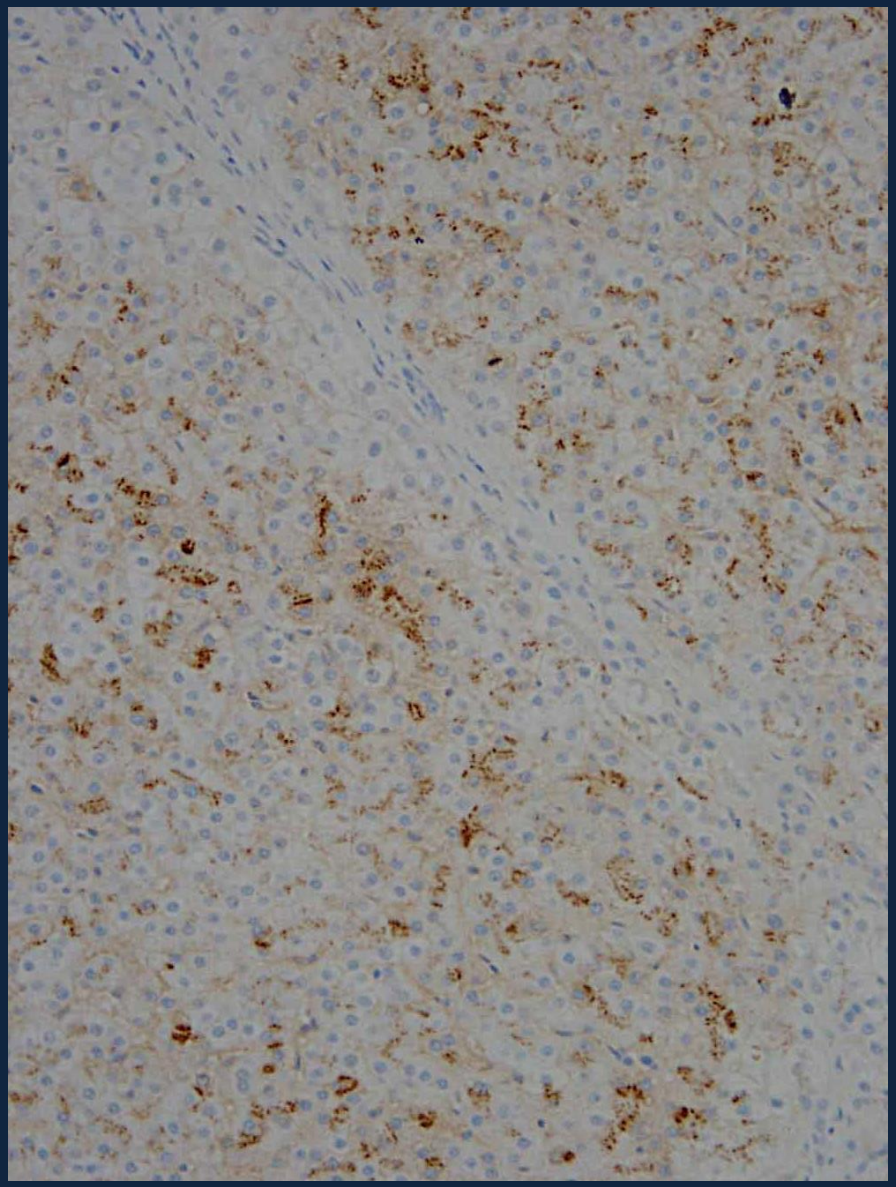
CRP: periseptal staining



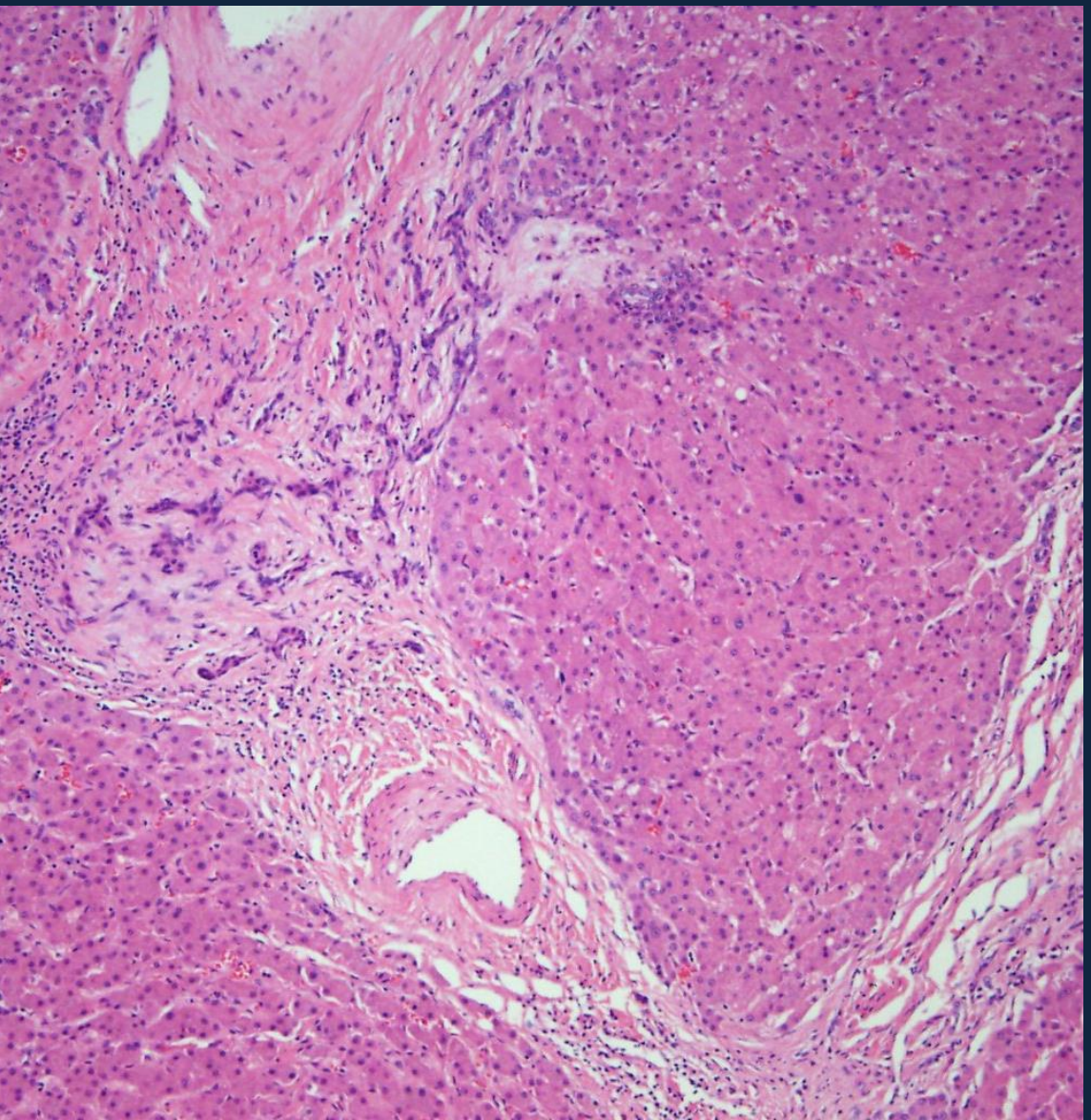
HE stain

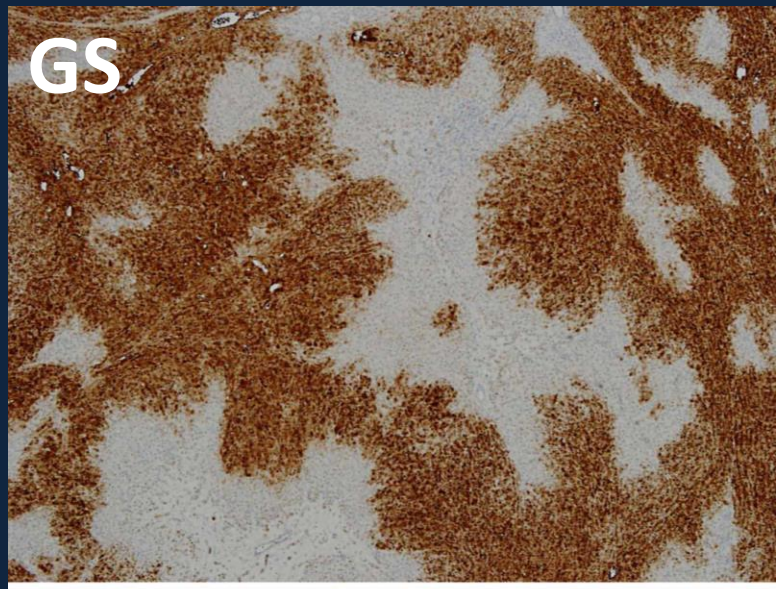


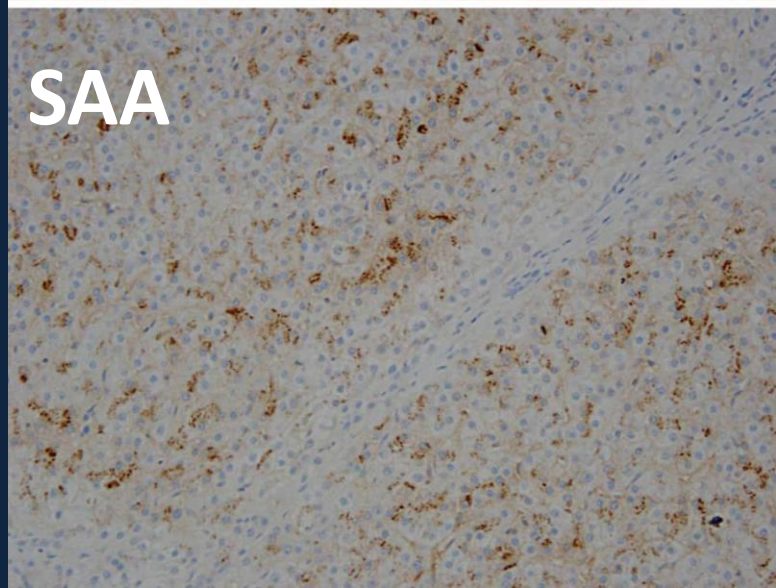
SAA+

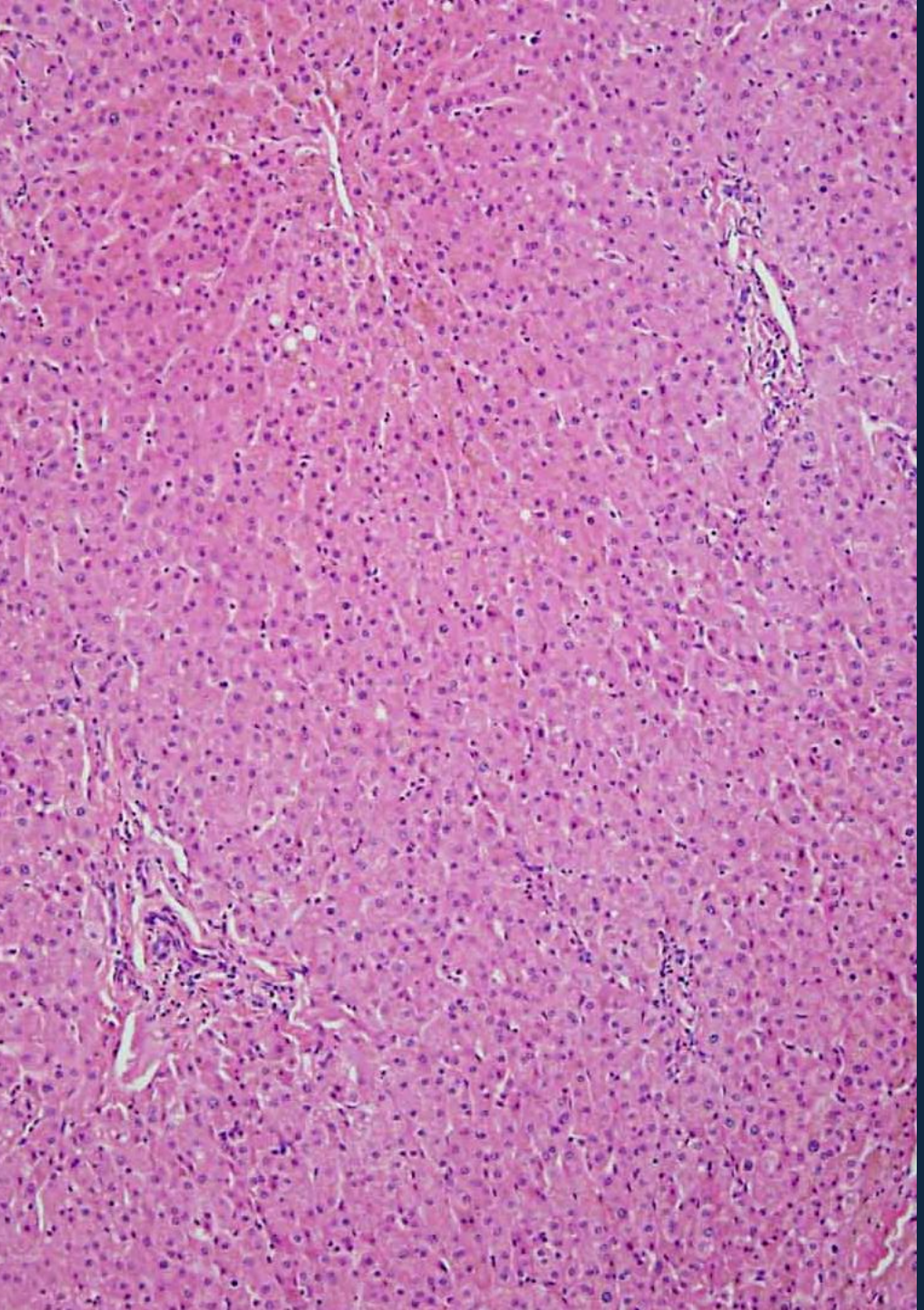


FNH with map-like GS and SAA+

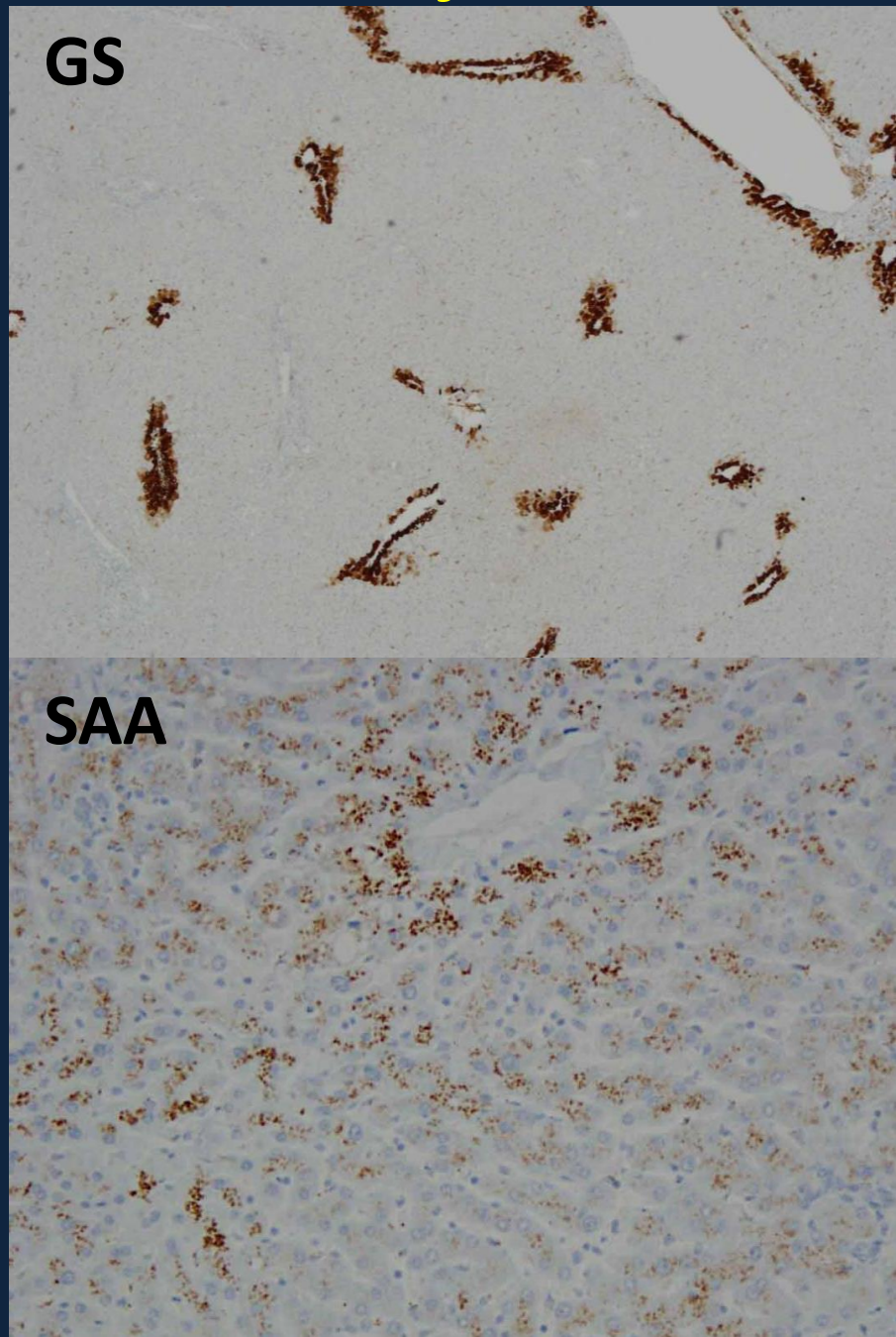


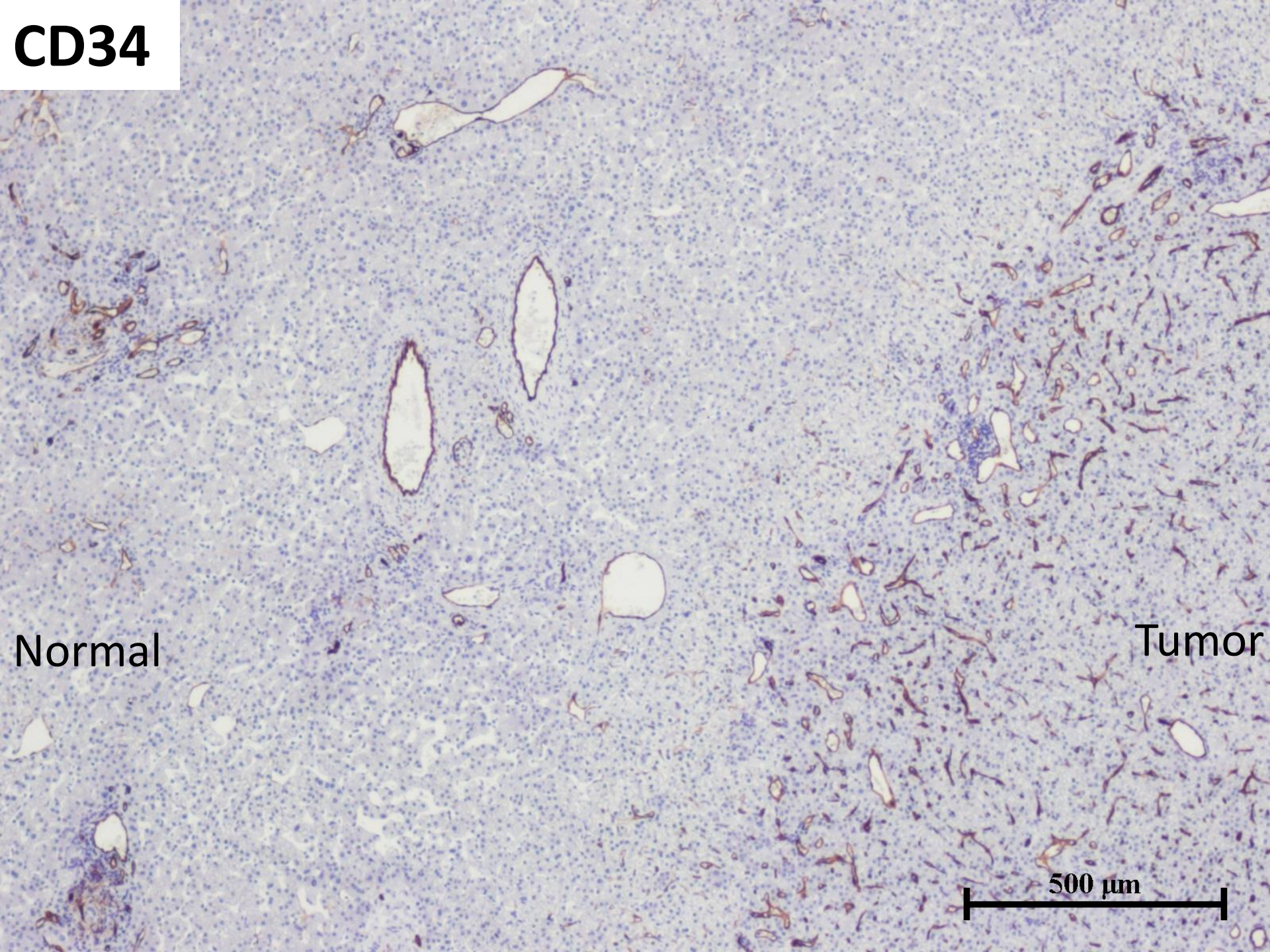






SAA+ in adjacent liver



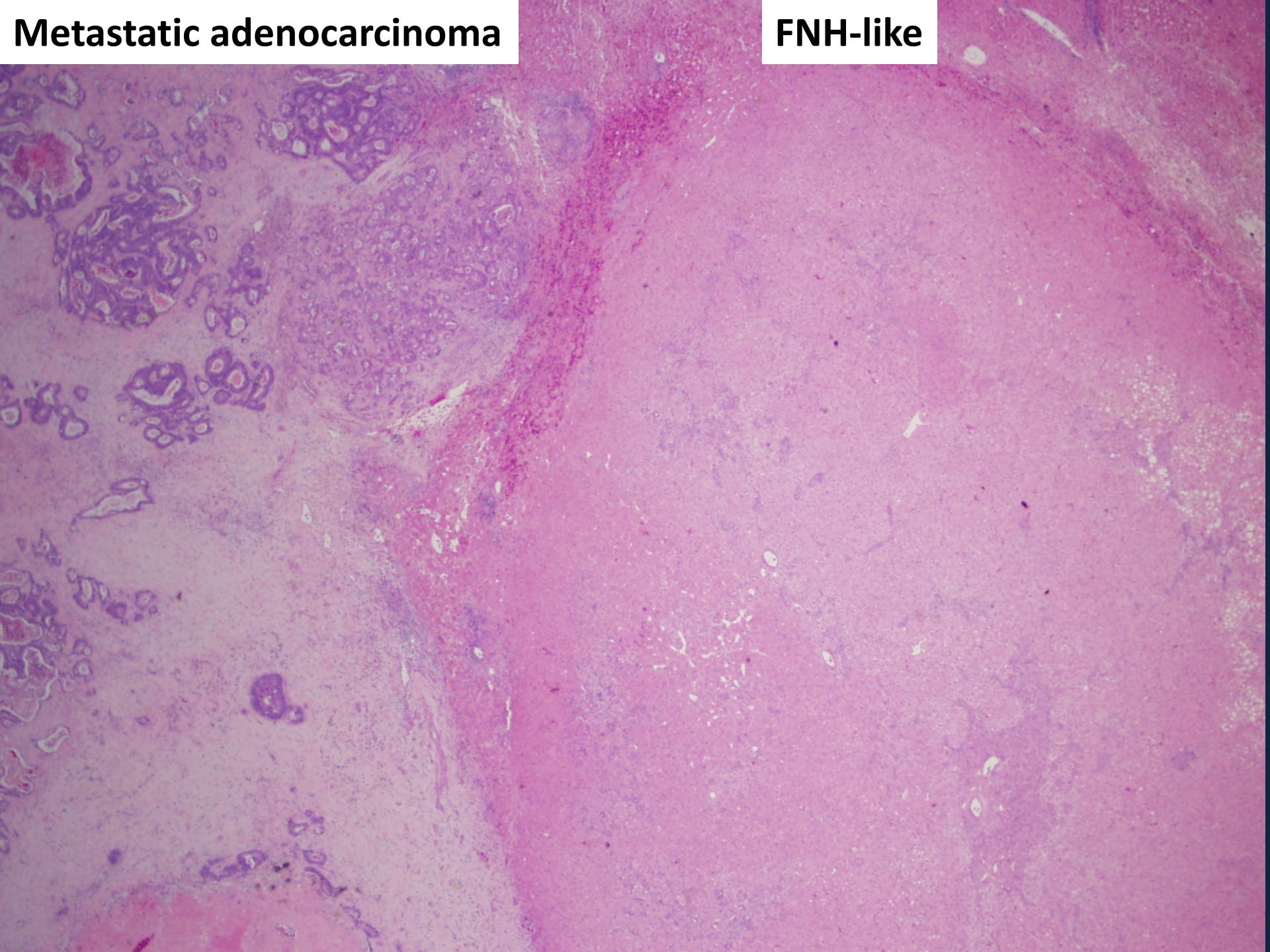

CD34
Normal
Tumor
500 µm

“FNH-like lesion”: two settings

-Lesions with lack of well-developed features

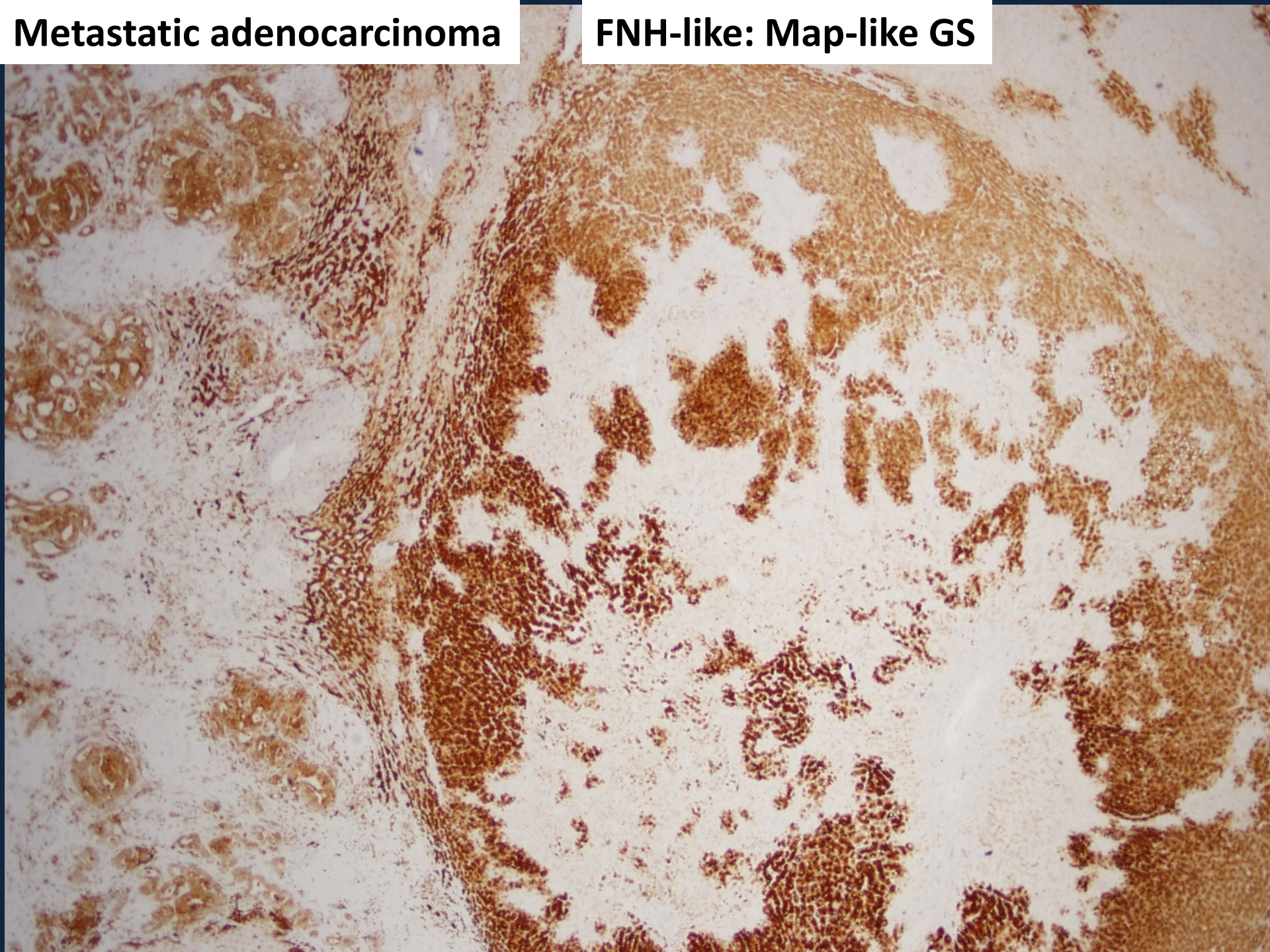
-Morphology and GS staining similar to classic FNH

- Adjacent to tumors
- Cirrhosis
- Vascular tumors, Budd-Chiari syndrome


Metastatic adenocarcinoma
FNH-like

Metastatic adenocarcinoma

FNH-like: Map-like GS



Practical considerations: summary

Diagnostic Challenge	Approach
I-HCA and FNH: overlapping features	Essential stains: GS, SAA Others, if required
GS, SAA interpretation	Map-like GS: FNH SAA/CRP can be focally positive in FNH
SAA, CRP positive in adjacent liver	Focus on morphology Obtain CD34 stain
FNH-like	Adjacent to other masses Vascular tumors/malformations Vascular diseases (Budd-Chiari syndrome)

β-catenin-activated hepatocellular neoplasms

- Association with HCC
  - Frequent cytologic atypia
  - Frequent loss of reticulin
- Cytogenetic changes like HCC

Zucman-Rossi, Hepatol 2006
Bioulac-Sage, Hepatol 2007
Evason/Kakar, Hum Pathol 2013

β-catenin-activated hepatocellular neoplasms

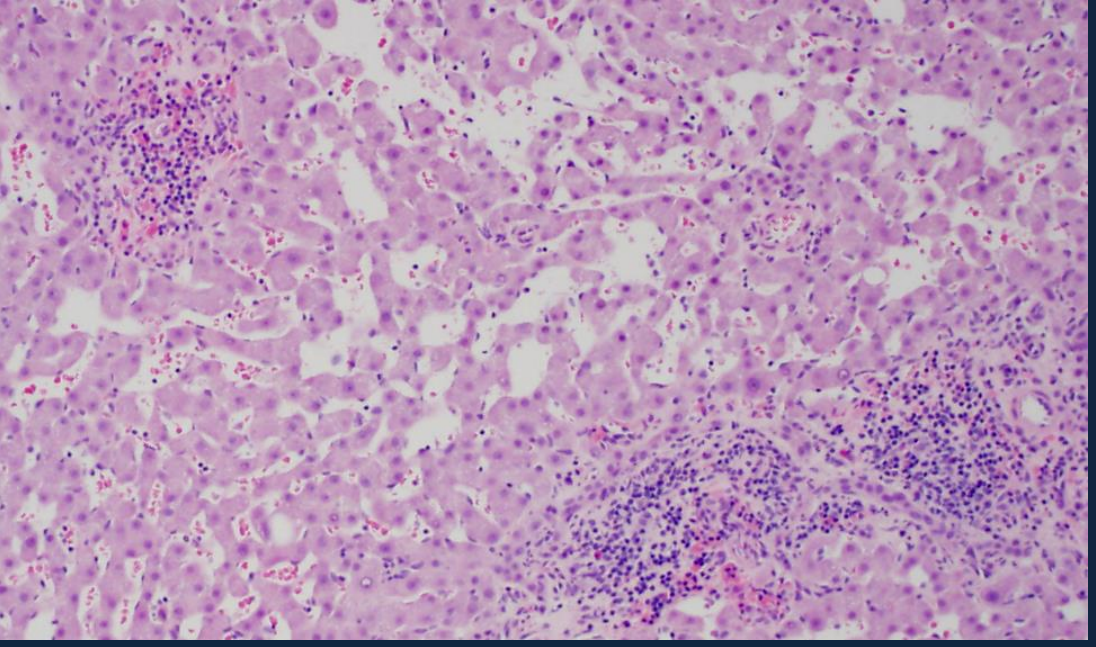
HCA

HNF1α | Inflammatory | Unclassified

Atypical

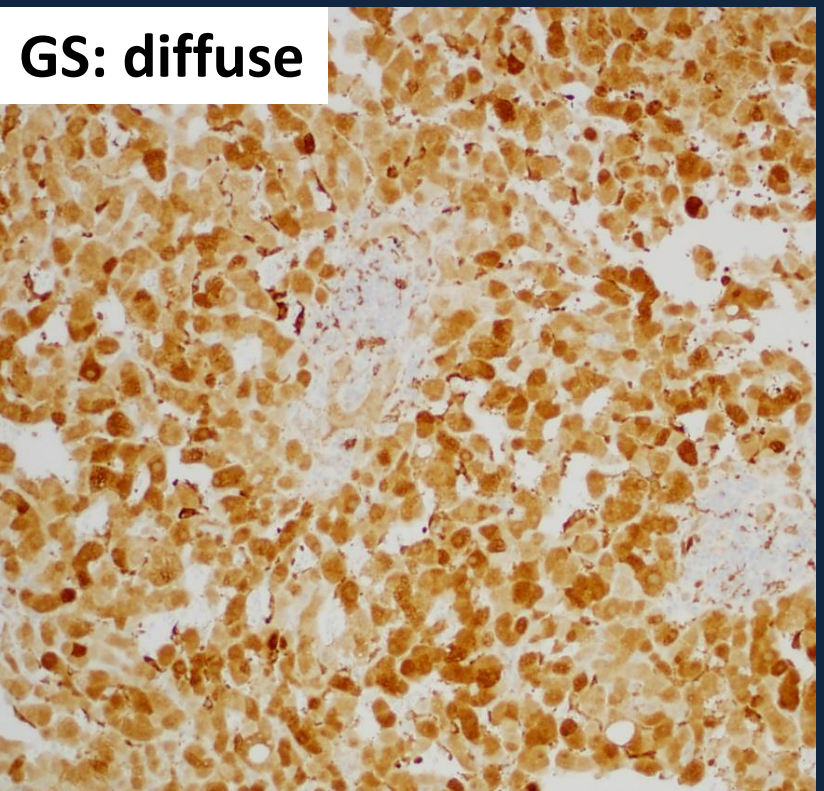
HCC

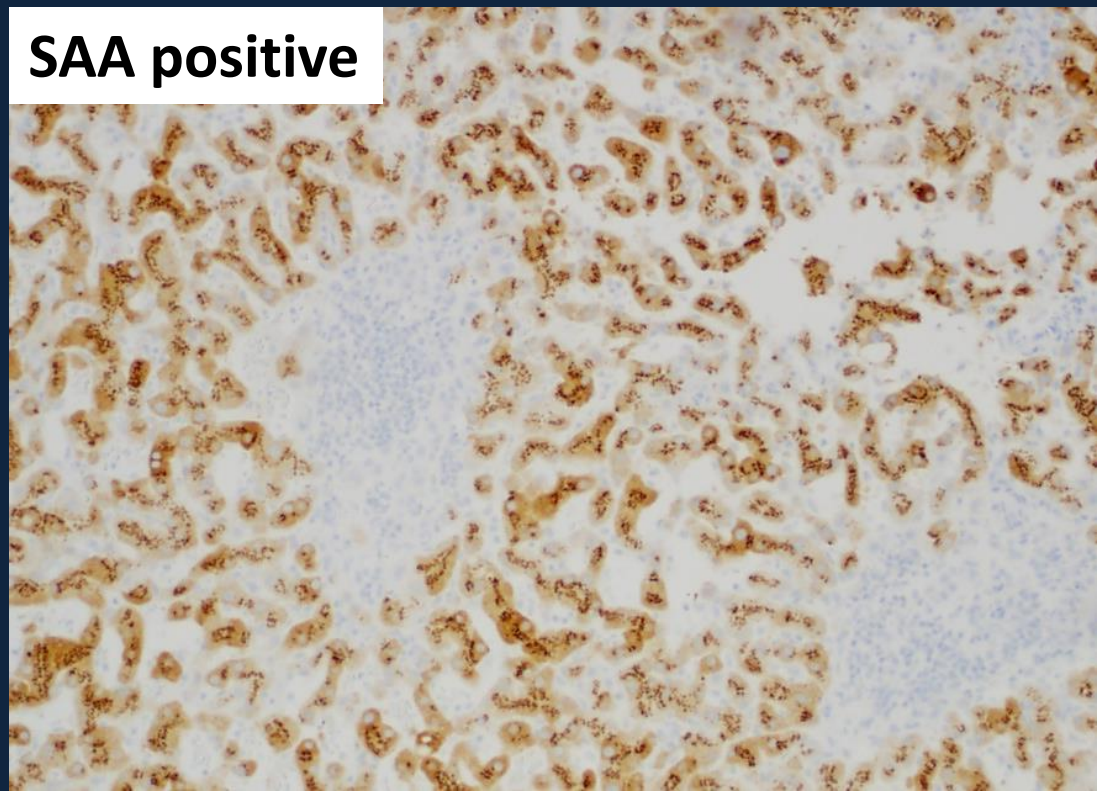
β-catenin activation



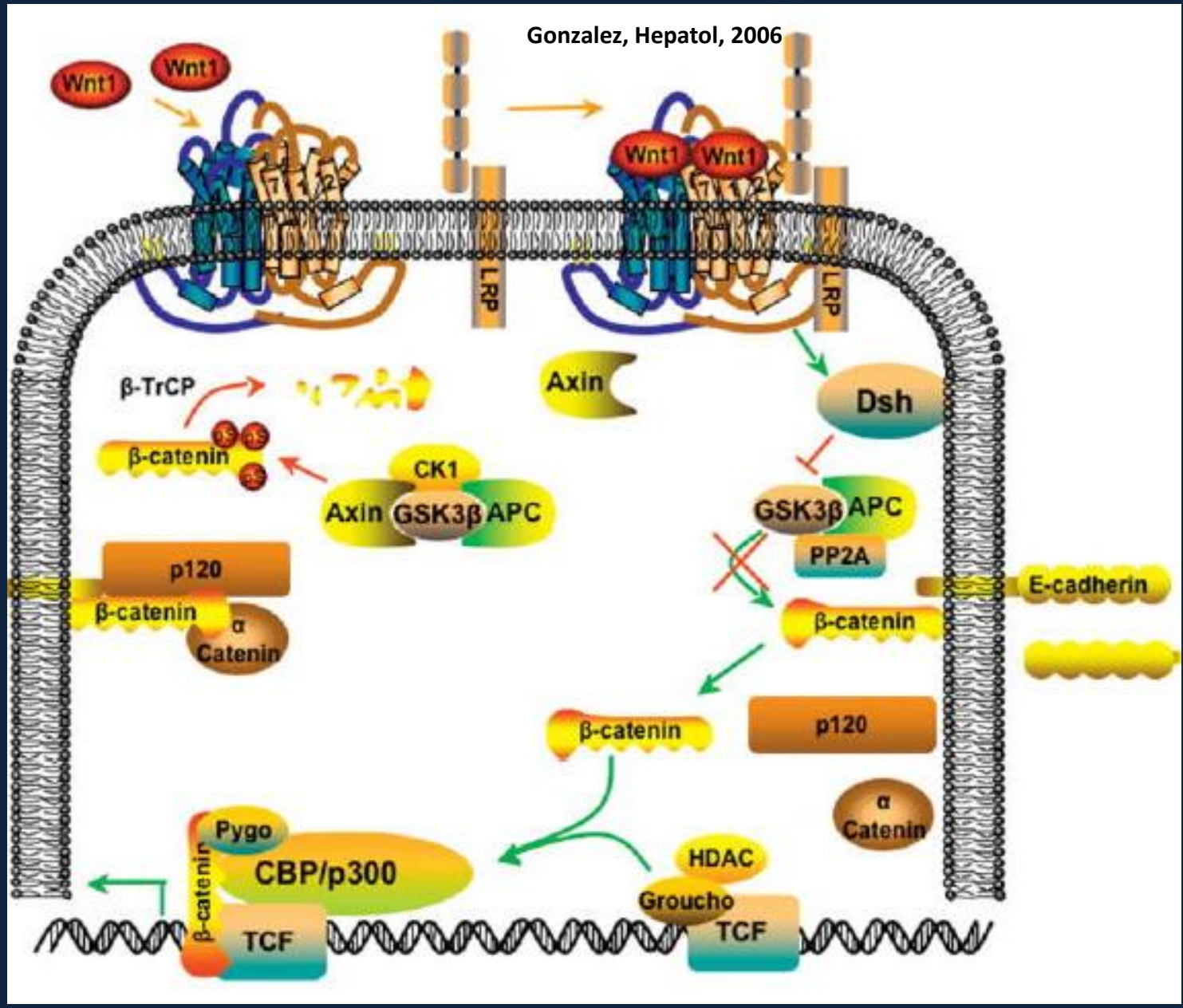
Inflammatory HCA with β-catenin activation

- 10% of cases
- High risk feature



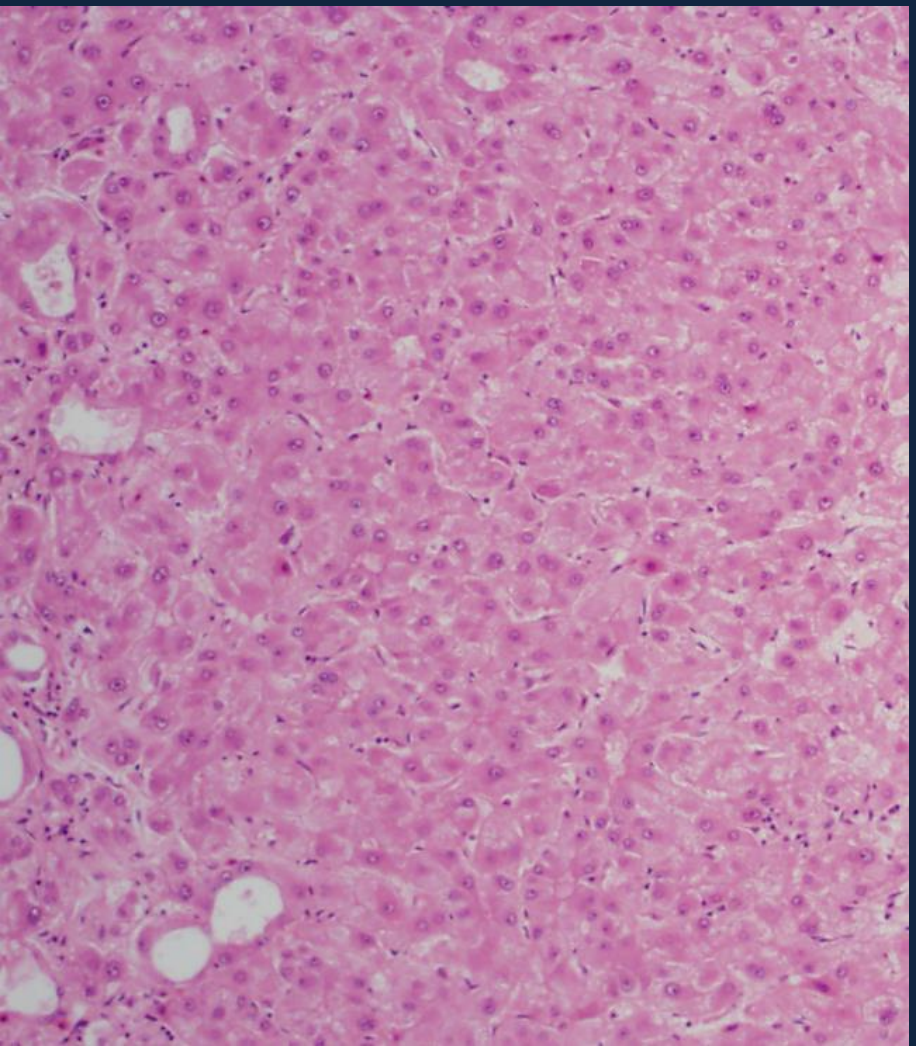


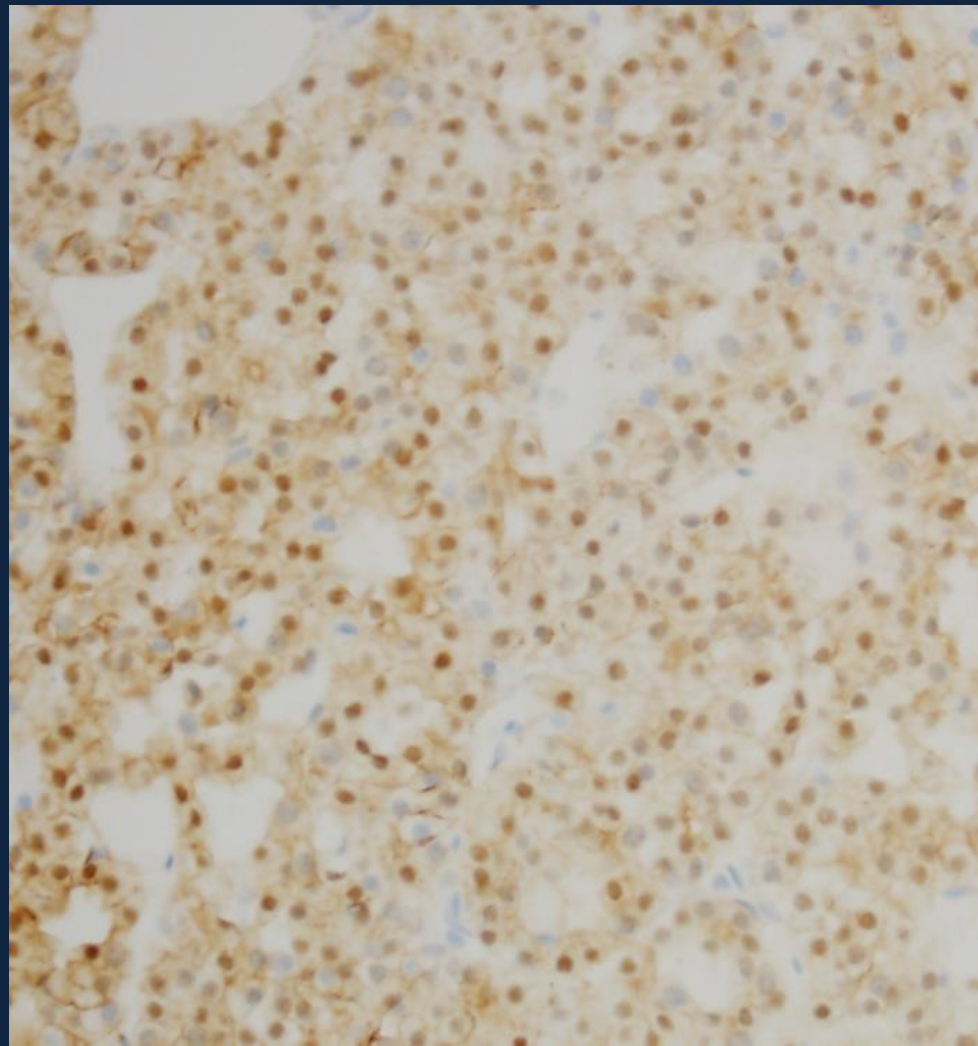
Wnt signaling pathway



Hepatocellular neoplasm with exon 3 β-catenin mutation

-Nuclear translocation of β-catenin



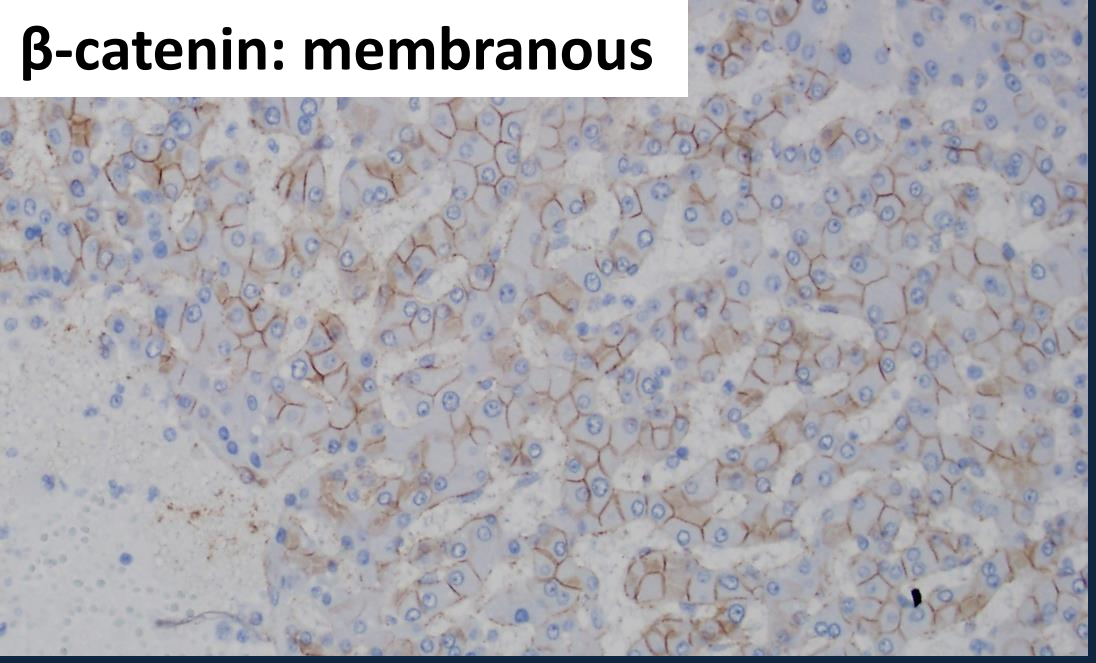


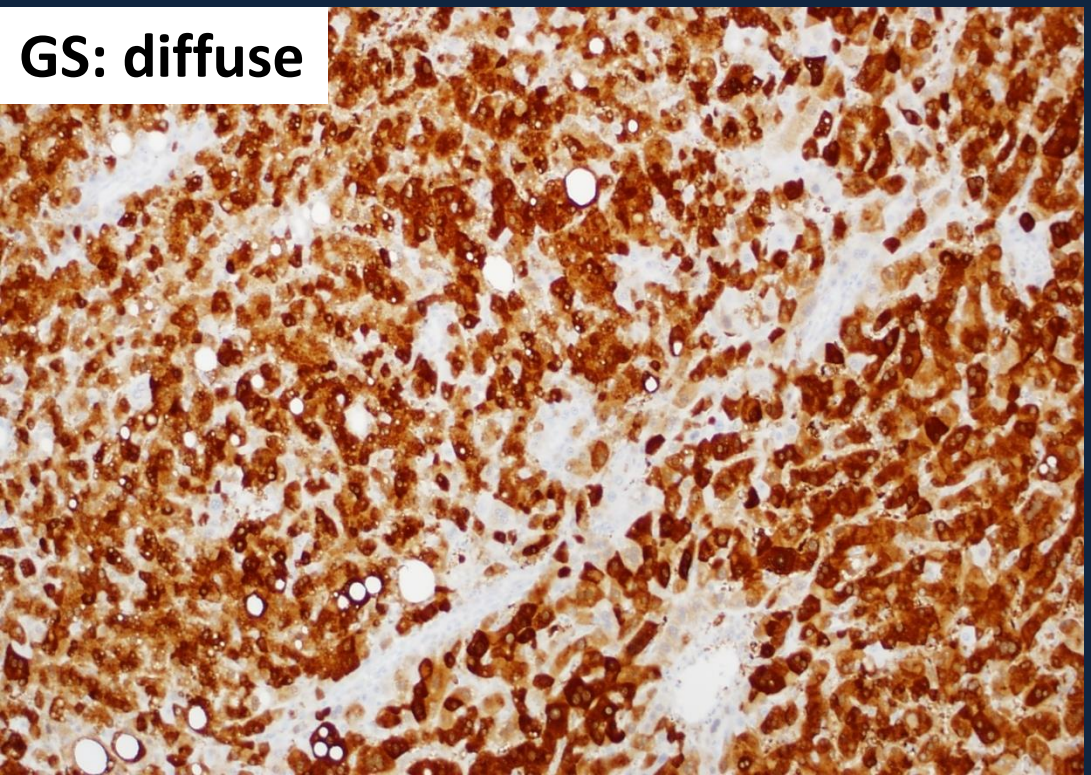
β-catenin activation

- β-catenin mutation present
  - 70% HCC: nuclear β-catenin
  - 20% adenomas/atypical: nuclear β-catenin
- Diffuse GS staining
  - Better correlates with β-catenin activation

Hale/Kakar, Mod Pathol 2016

Bioulac-Sage, Hepatol 2007





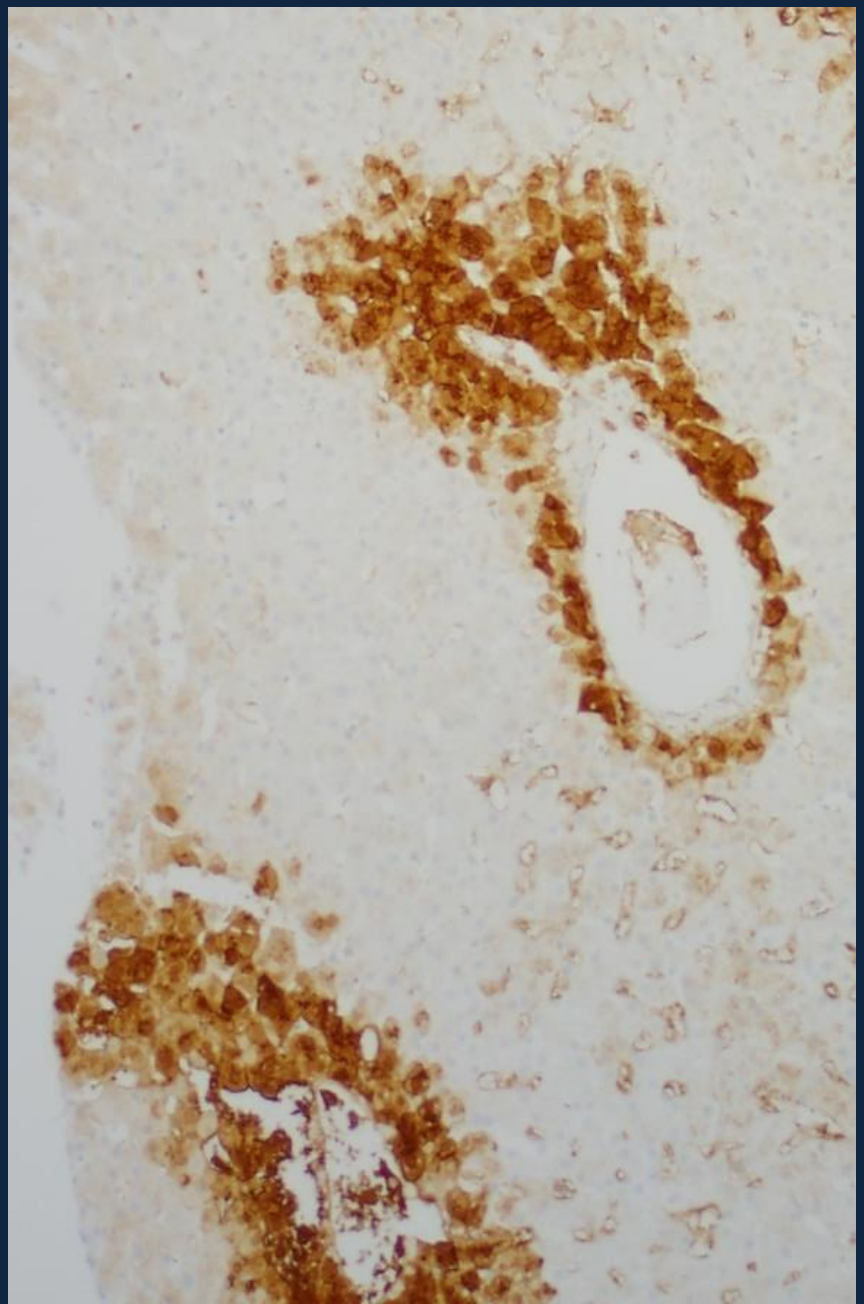
β-catenin mutated

- No nuclear β-catenin
- Diffuse GS

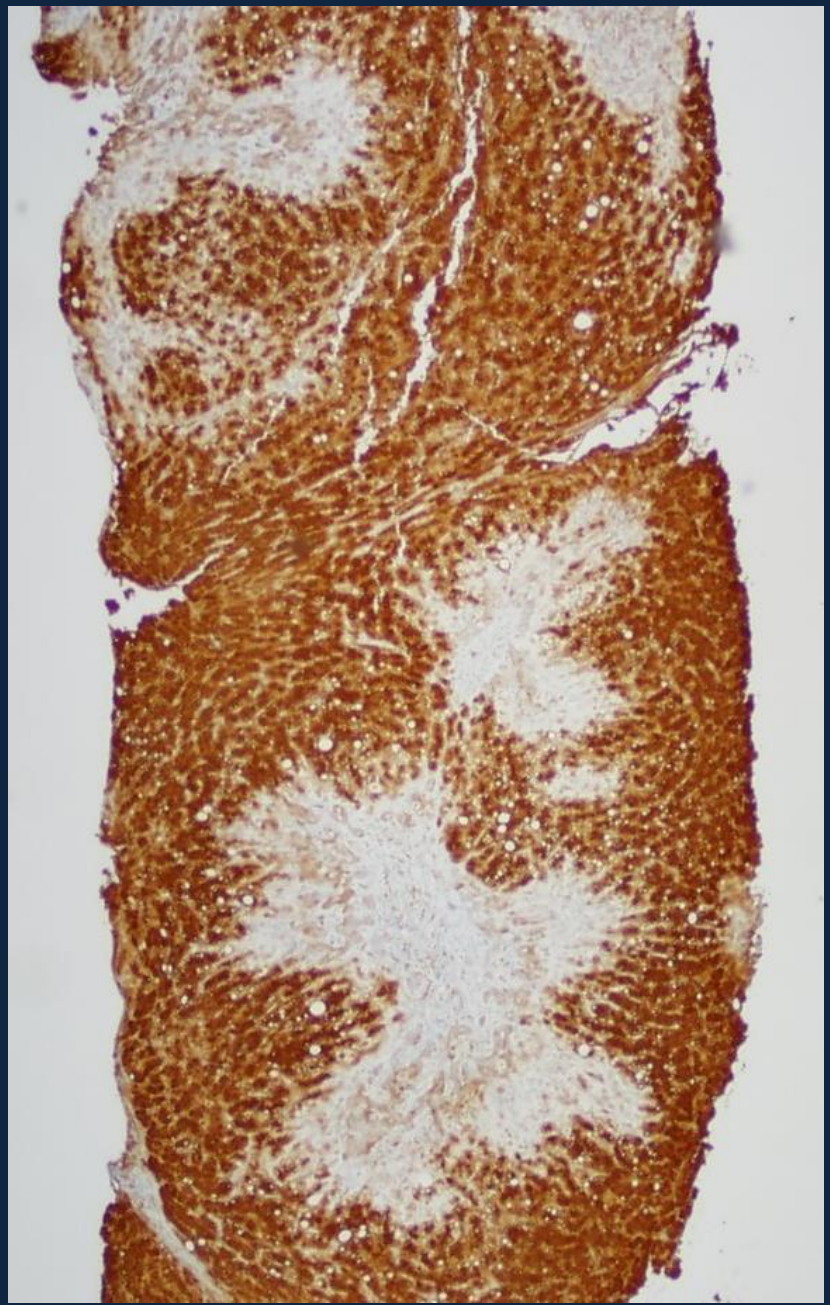
Interpretation of GS staining

- Spectrum of histologic patterns
- Definition and pitfalls in interpretation of diffuse GS

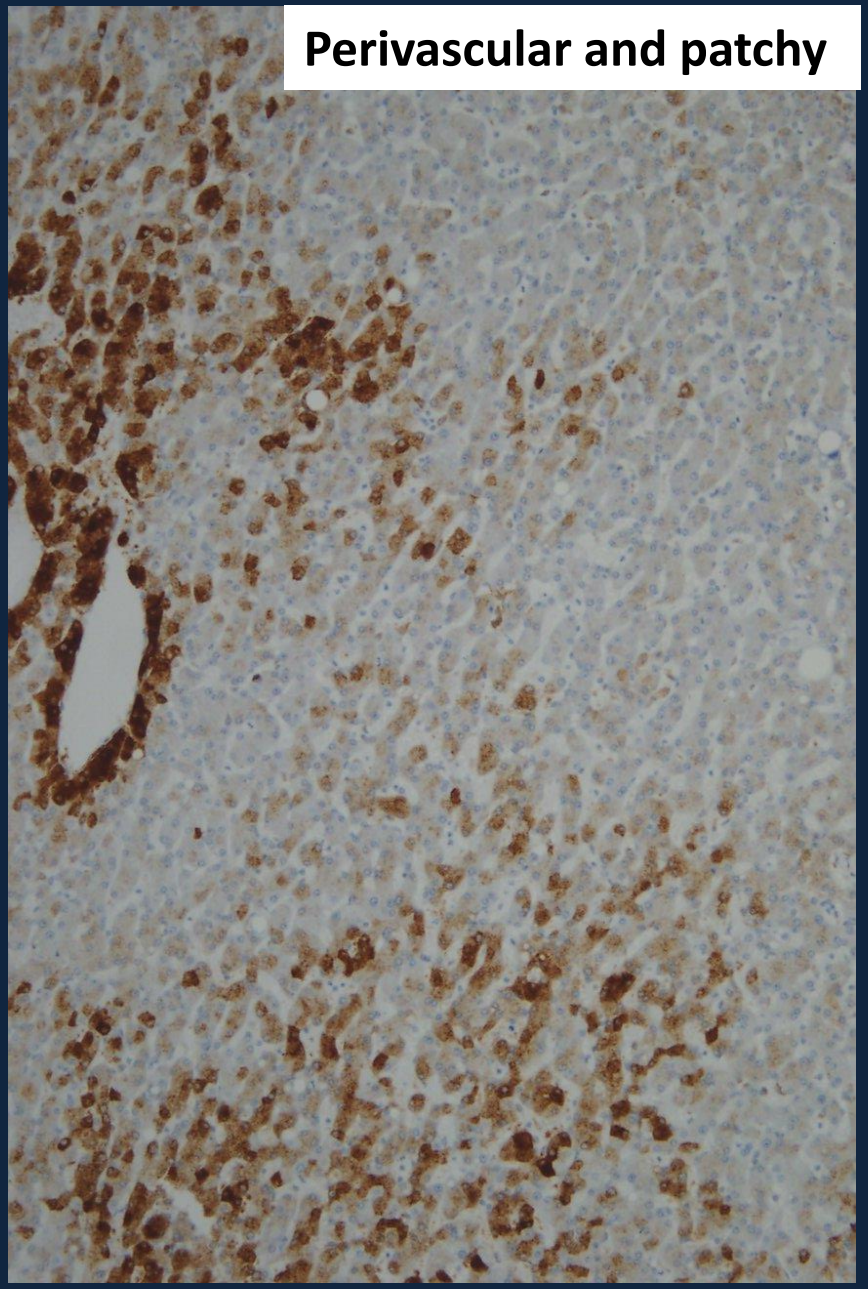
GS: normal

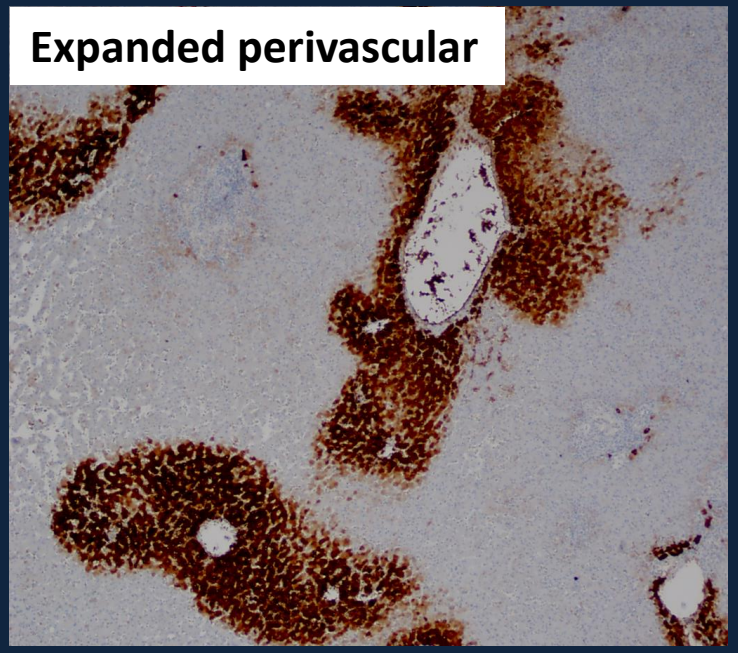


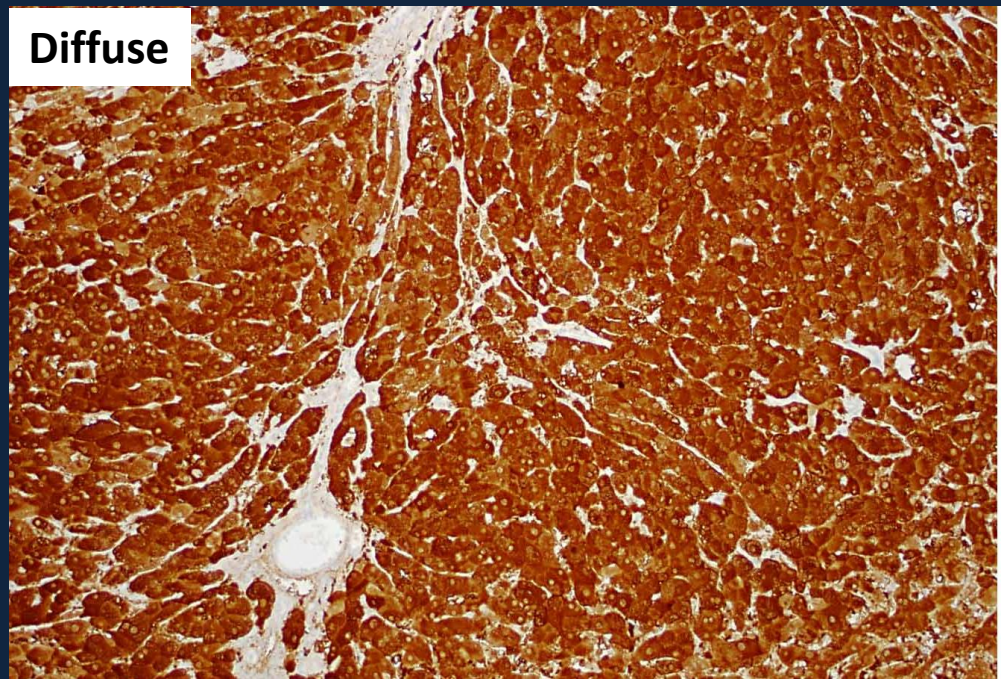
GS: map-like in FNH



GS patterns in adenoma







Hepatocellular Adenoma Subtype Classification Using Molecular Markers and Immunohistochemistry

Paulette Bioulac-Sage,*[1,2] Sandra Rebouissou,*[3,4] Cristel Thomas,[3,4] Jean-Frédéric Blanc,[2,5] Jean Saric,[6] Antonio Sa Cunha,[6] Anne Rullier,[1,2] Gaëlle Cubel,[2] Gabrielle Couchy,[3,4] Sandrine Imbeaud,[7] Charles Balabaud,[2,5] and Jessica Zucman-Rossi[3,4]

Definition of 'diffuse' GS staining:

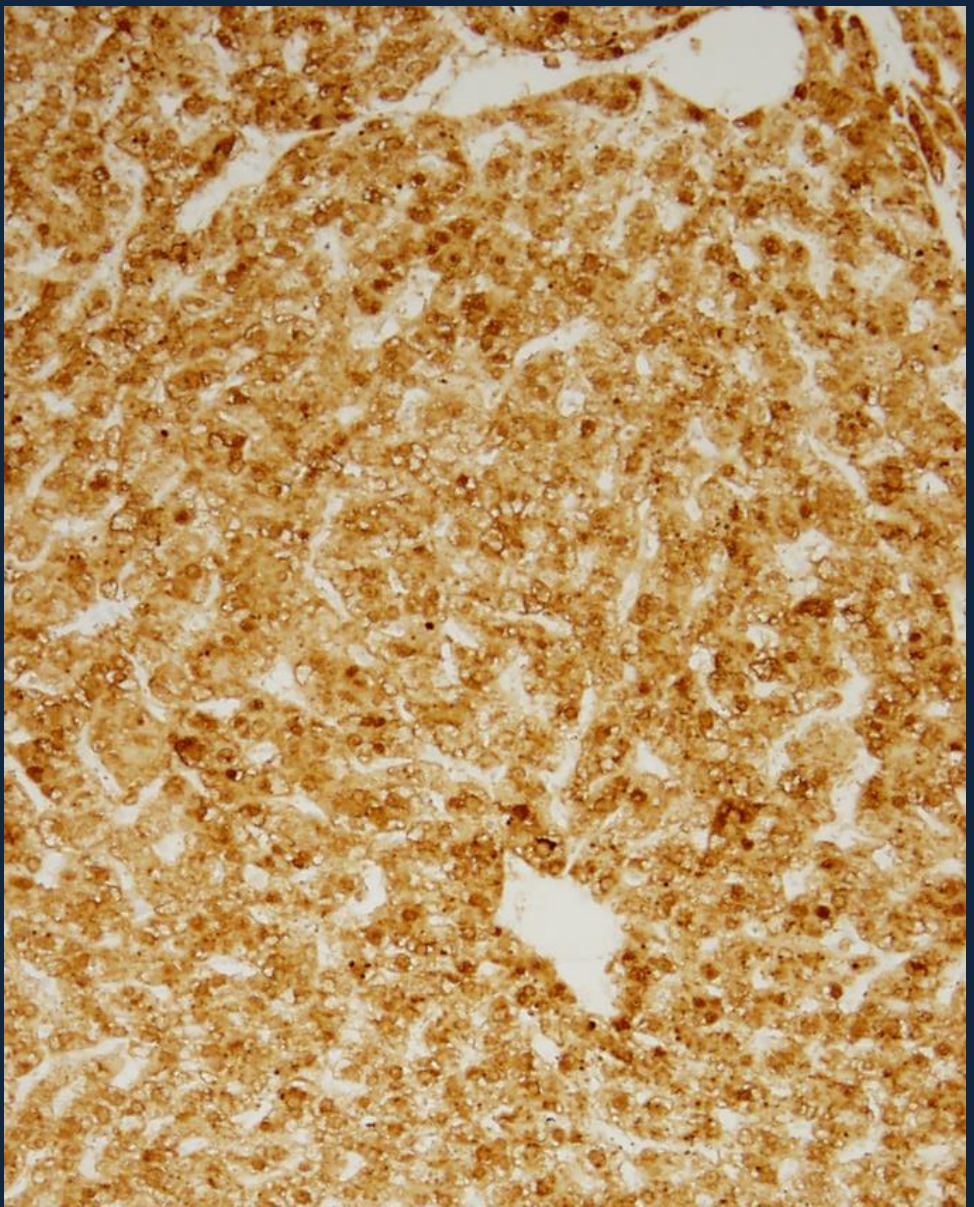
"Positive cytoplasmic overexpression, homogeneous or heterogeneous, but on >50% of tumor"

Patchy: Less than 50%

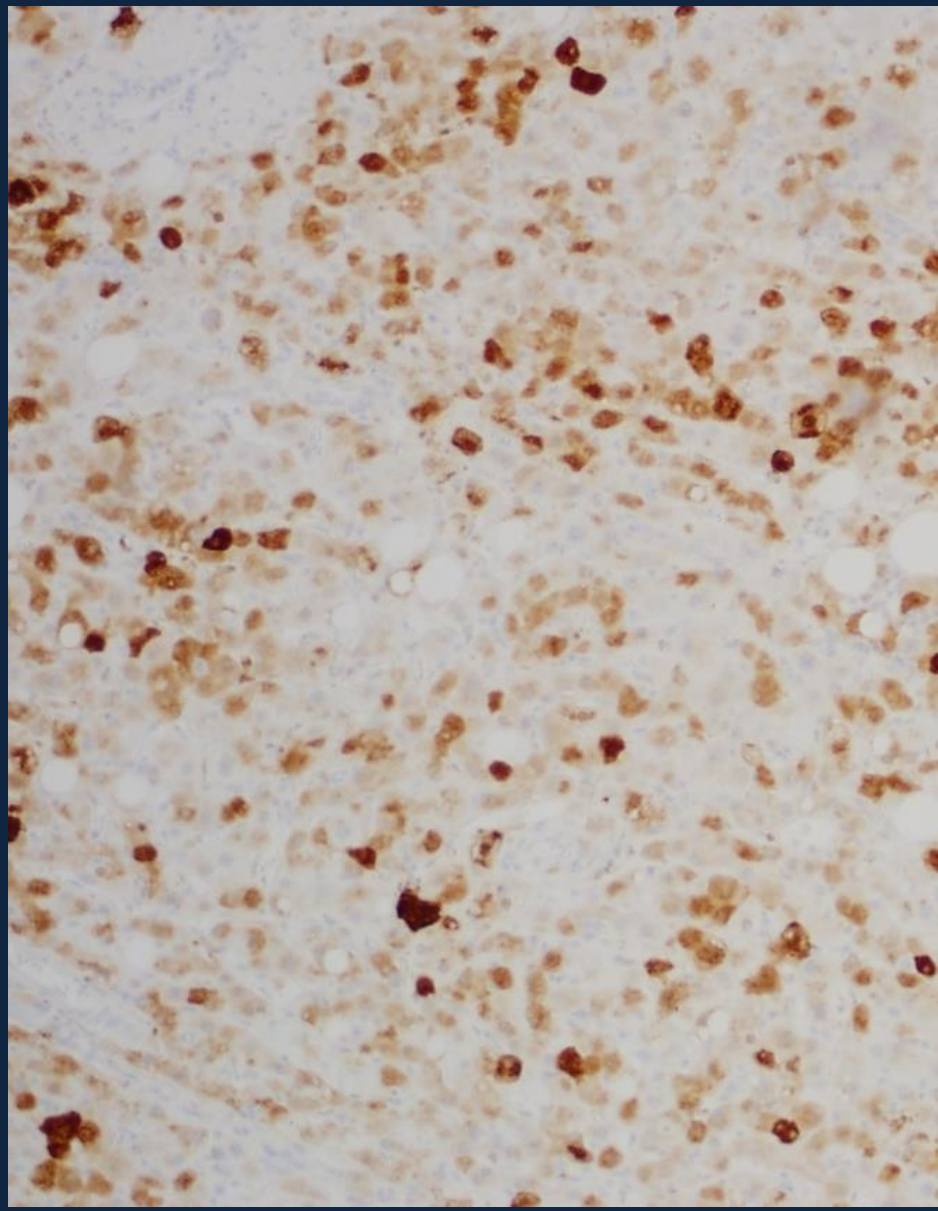
Zucman-Rossi, Oncol, 2007

Bioulac-Sage, Hepatology, 2007

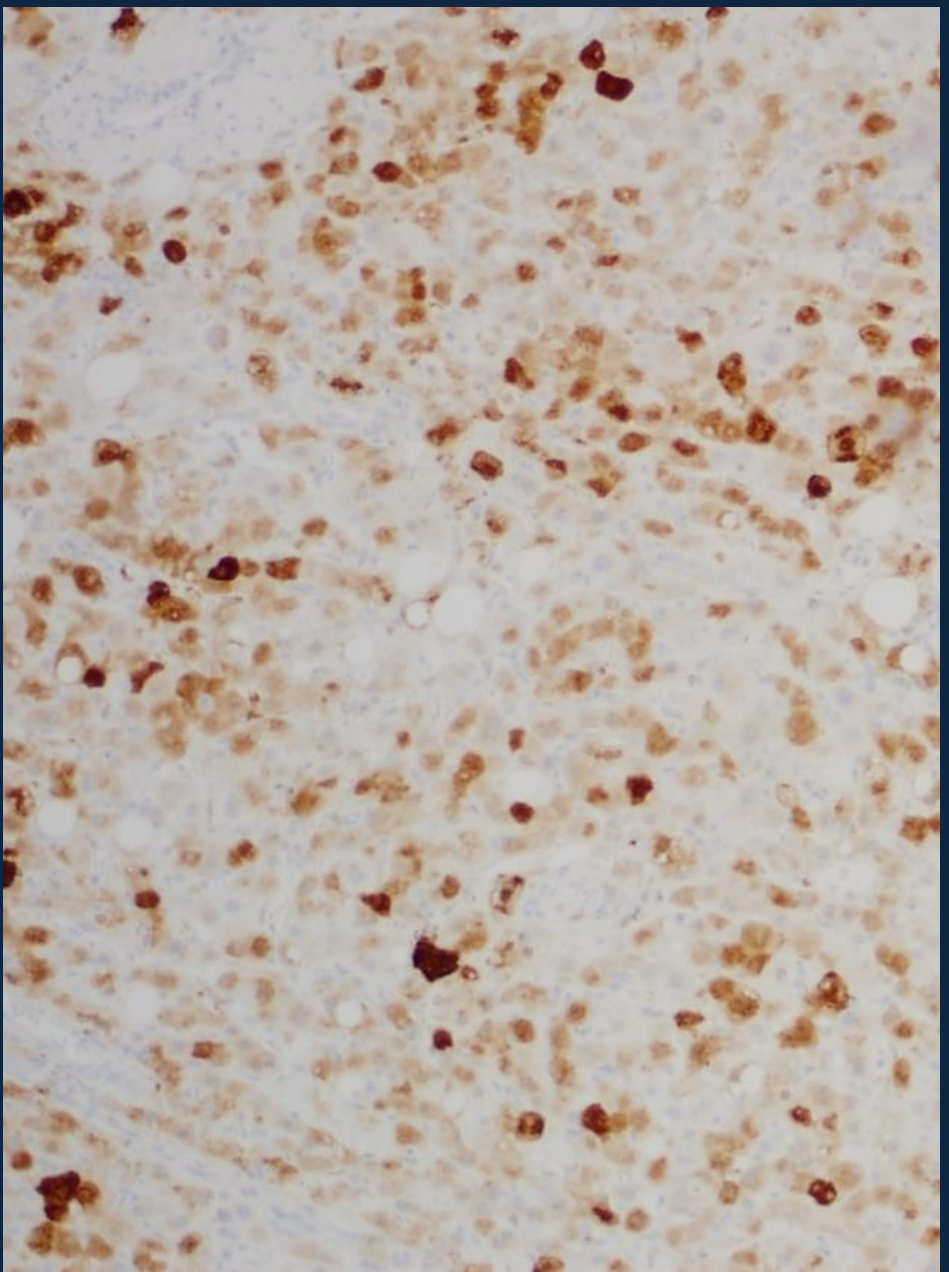
Diffuse homogeneous
GS ~100%

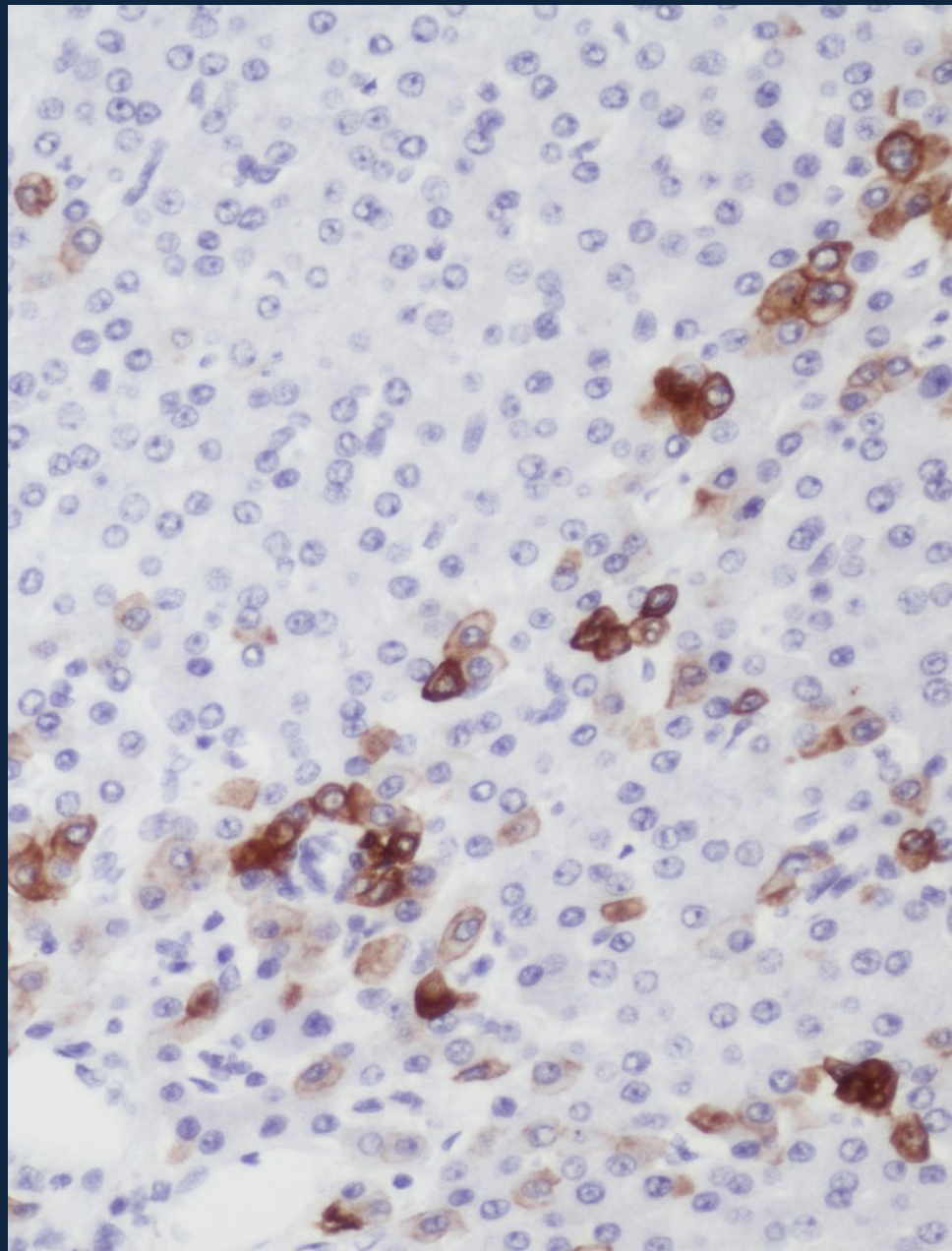


Diffuse heterogeneous
GS ≥50%

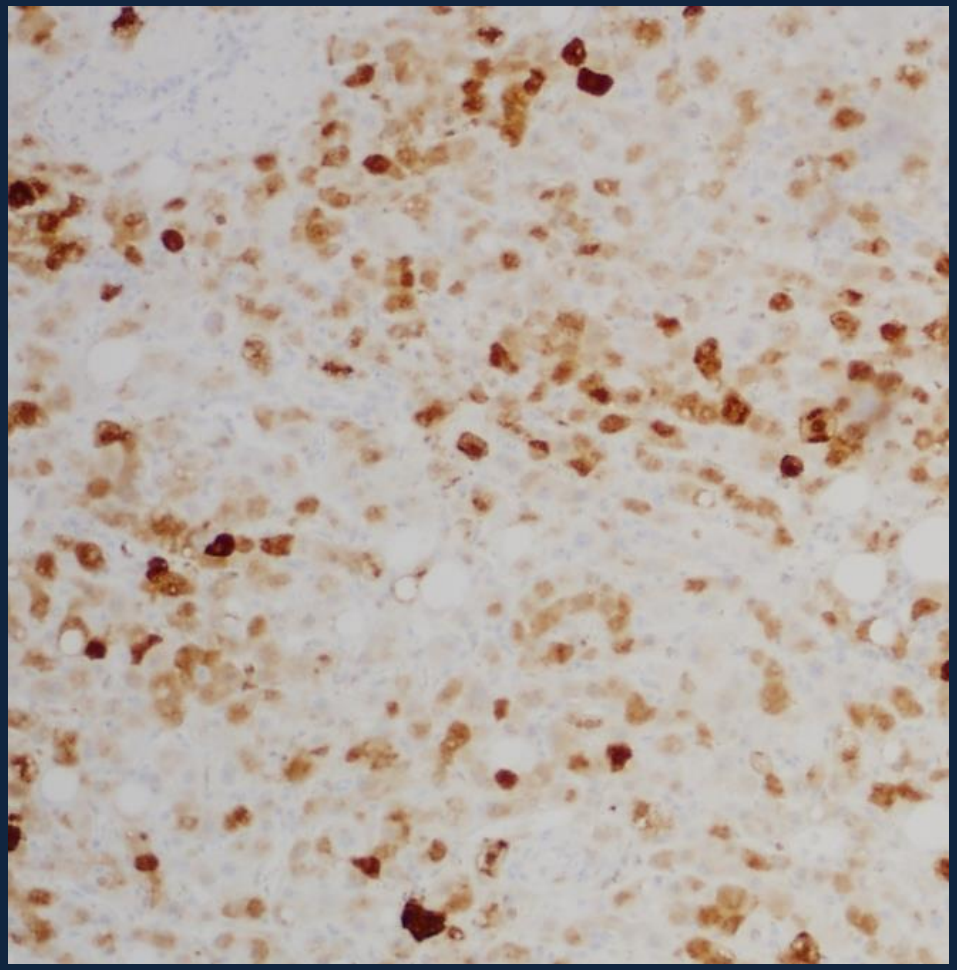


GS: diffuse heterogeneous (≥50%) vs. patchy staining (<50%)

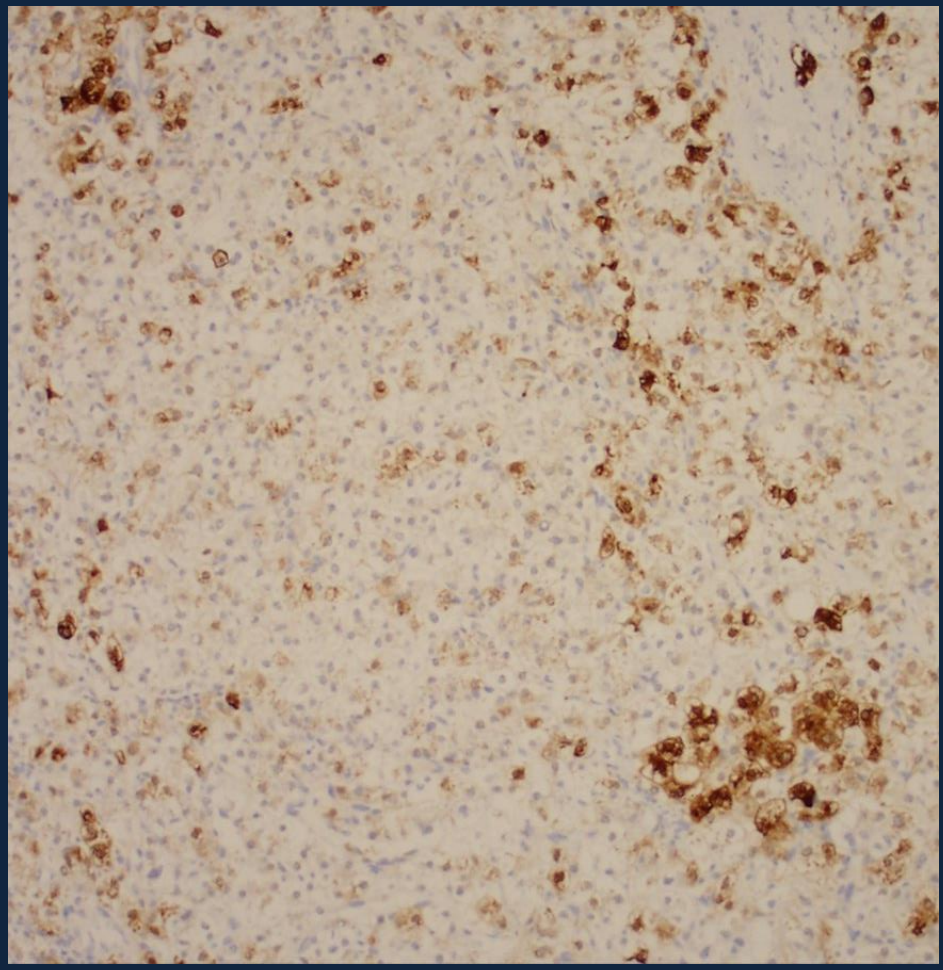




Diffuse GS ≥50%



<50% or ≥50%



GS staining patterns

Staining pattern	Interpretation
Diffuse homogeneous	Moderate to strong cytoplasmic staining >90% of lesional cells Likely β-catenin activation
Diffuse heterogeneous	Moderate to strong cytoplasmic staining in 50-90% of lesional cells Lower association with β-catenin activation
Patchy (not diffuse)	β-catenin activation very unlikely
Indeterminate	Indefinite for β-catenin activation

β-catenin-activated hepatocellular neoplasms

HCA

HNF1α | Inflammatory | Unclassified

Atypical

HCC

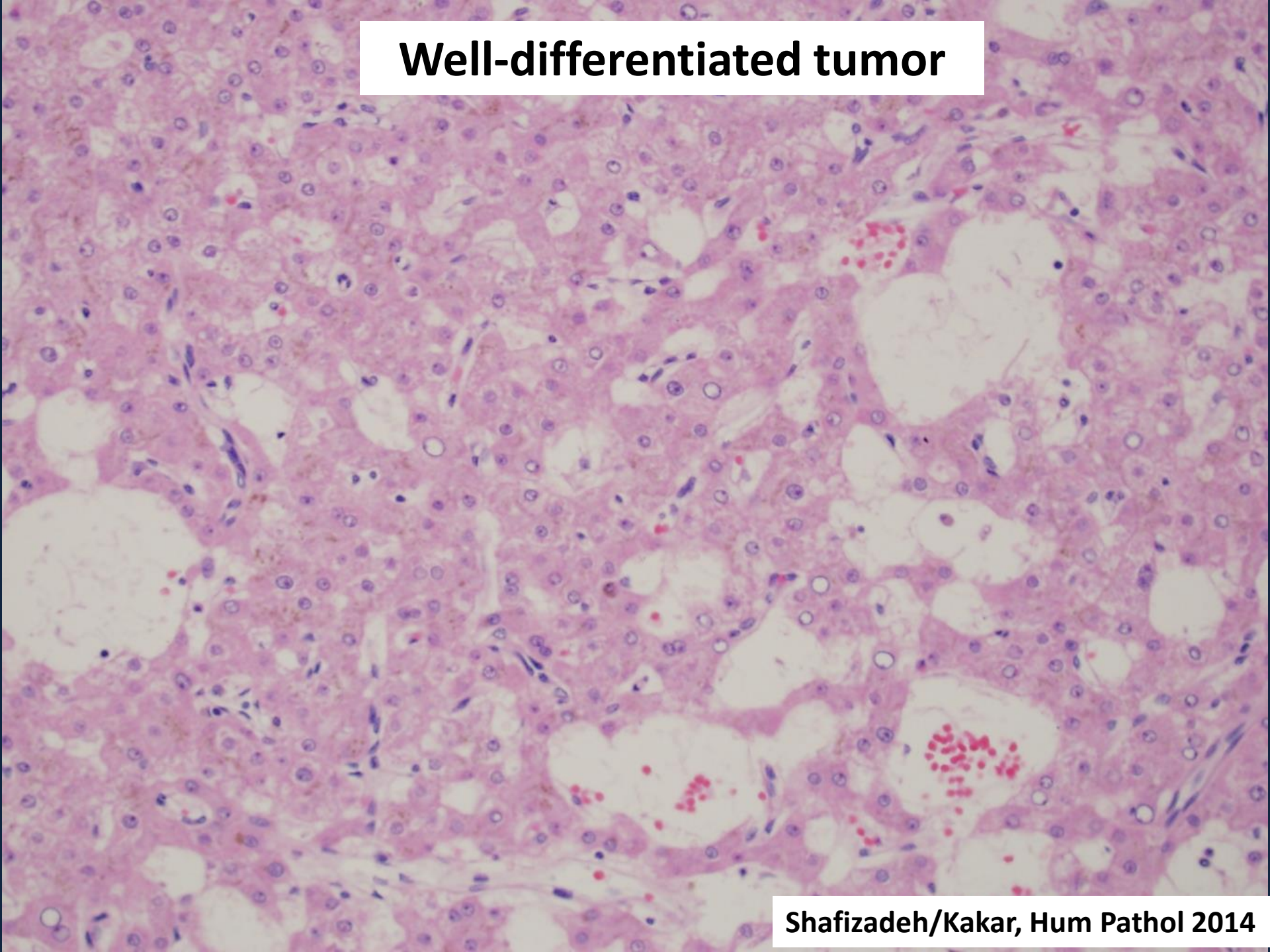
β-catenin activation

Atypical features

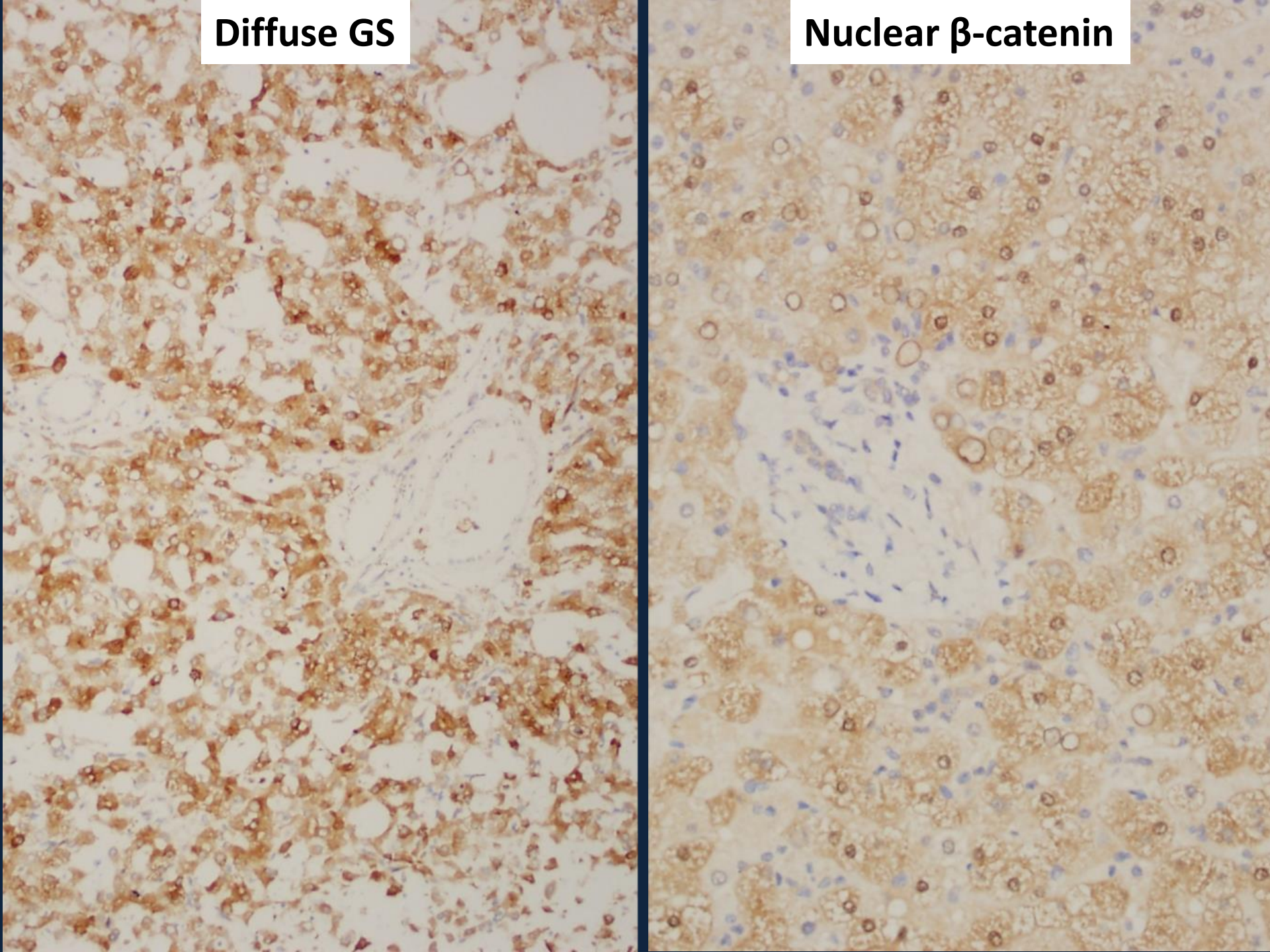
Clinical	**Male gender (any age)** **Age (>50 years)** **Glycogen storage diseases, androgen use**
Morphologic	**Focal cytologic atypia** **Focal reticulin loss** **Nuclear β-catenin, diffuse GS**

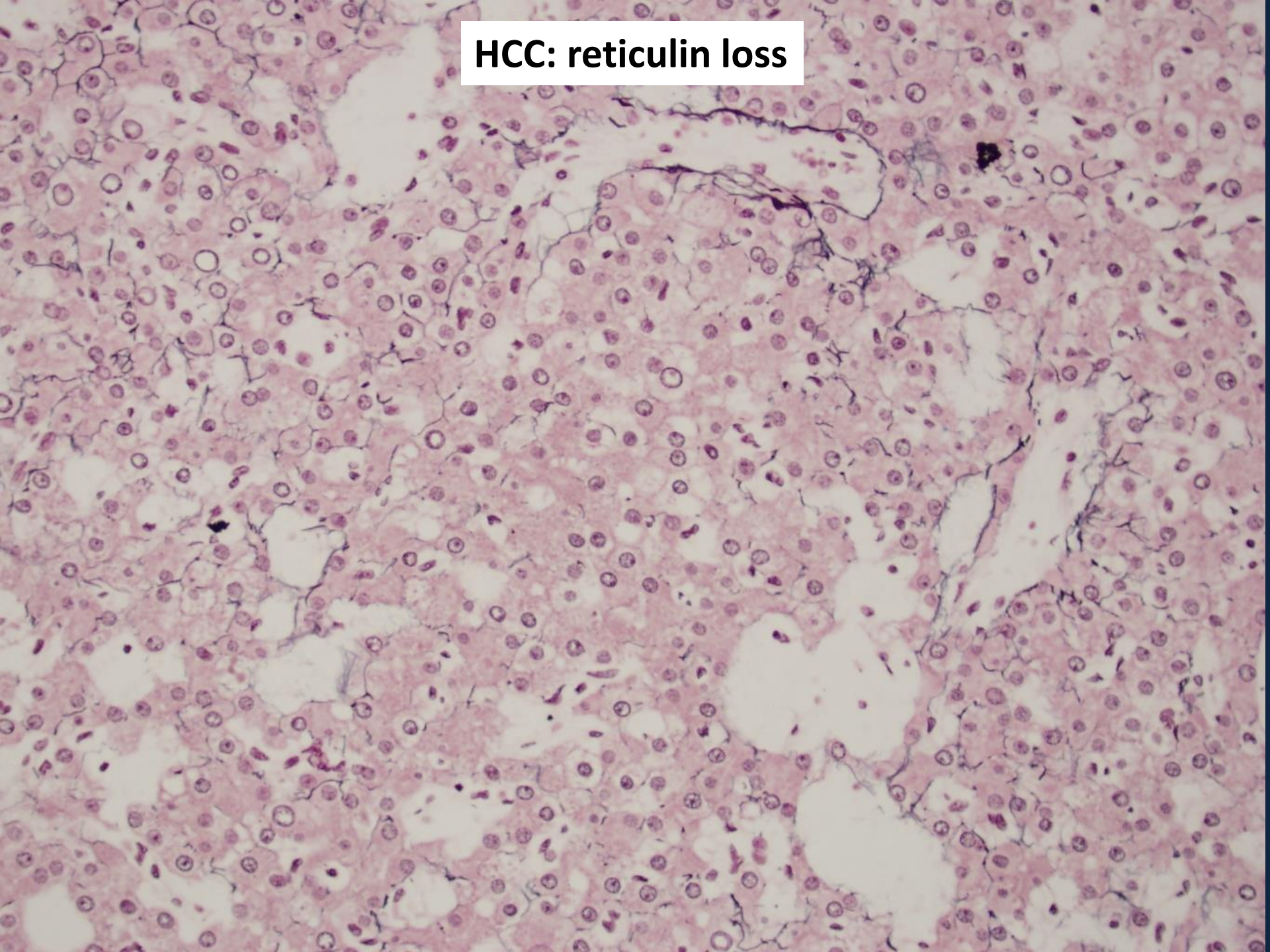
Bedossa, Hum Pathol 2014

Well-differentiated tumor

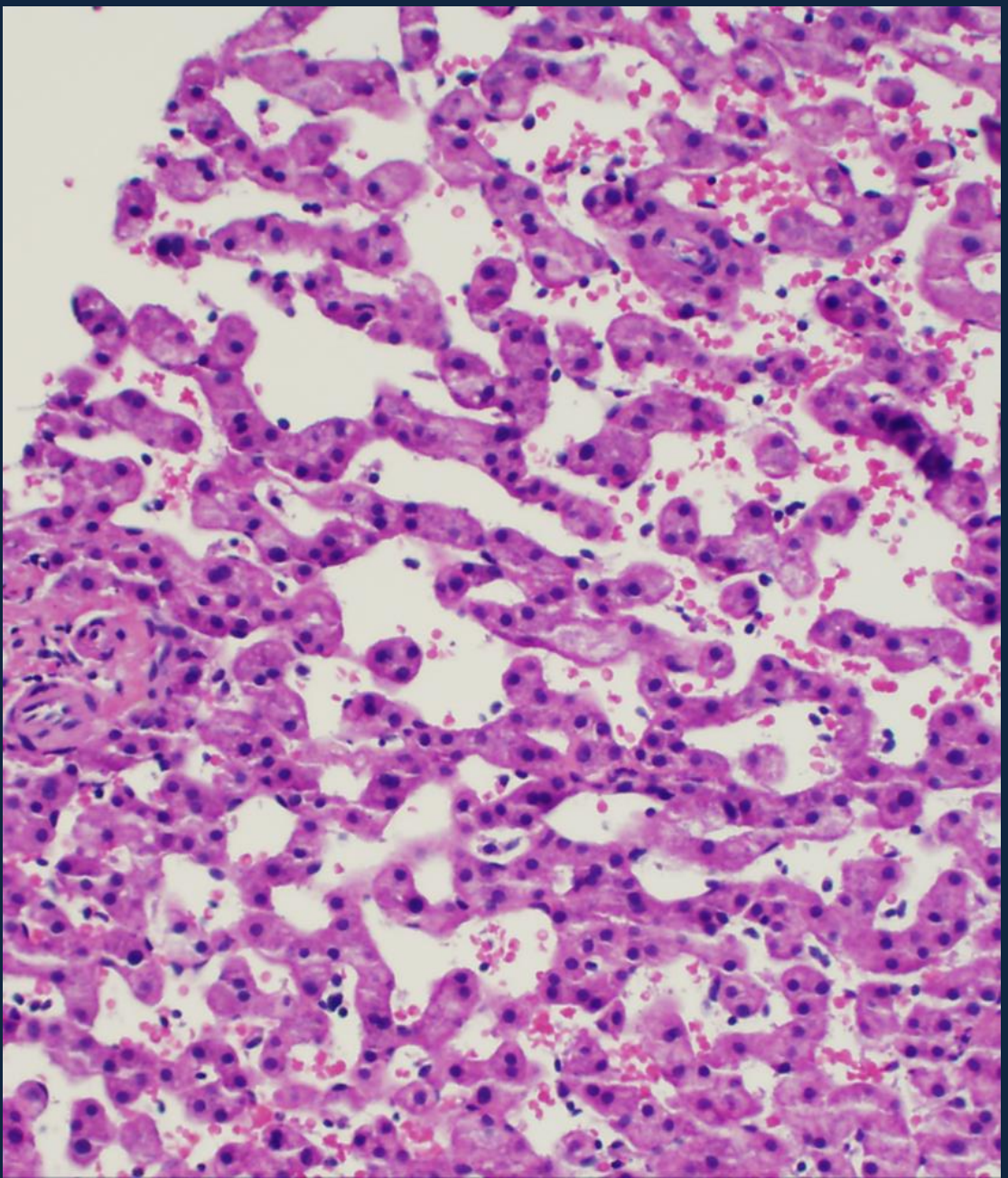


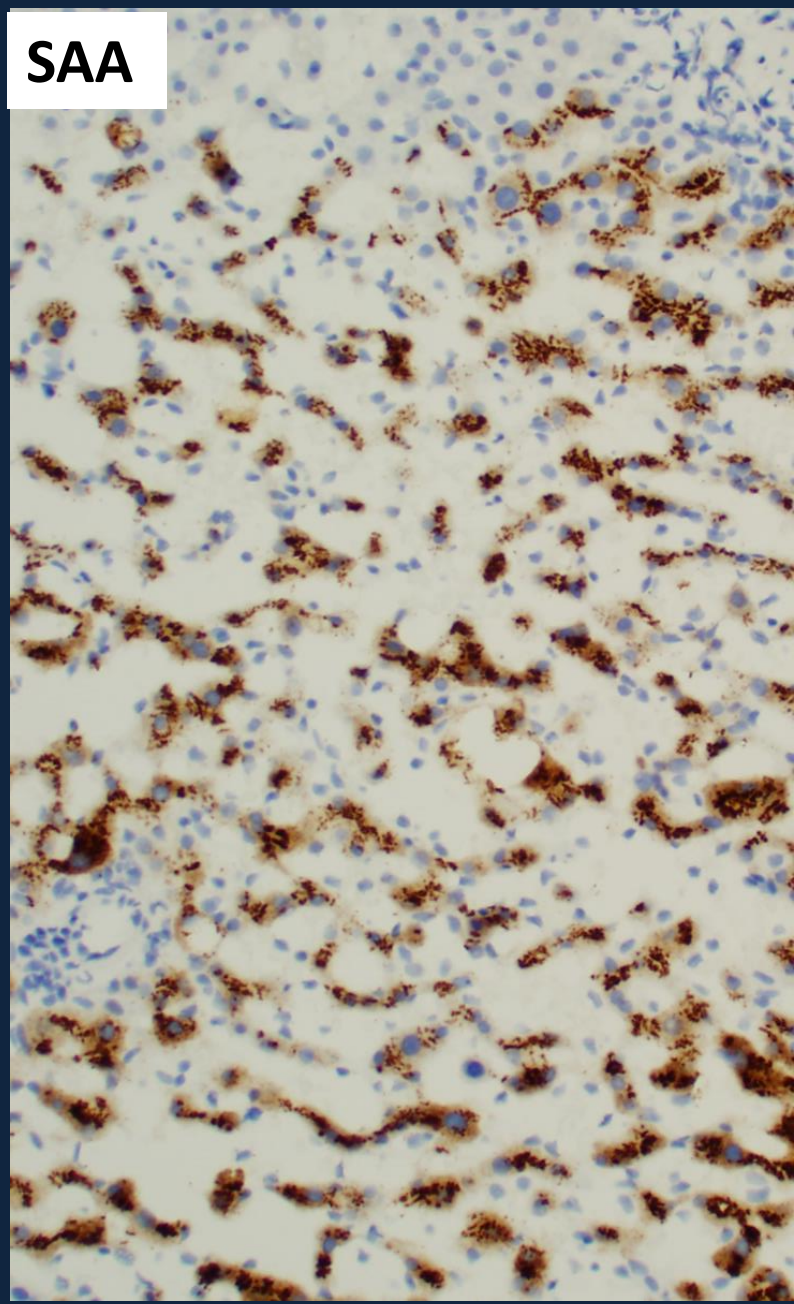
Shafizadeh/Kakar, Hum Pathol 2014


Diffuse GS
Nuclear β-catenin


HCC: reticulin loss

Inflammatory HCA

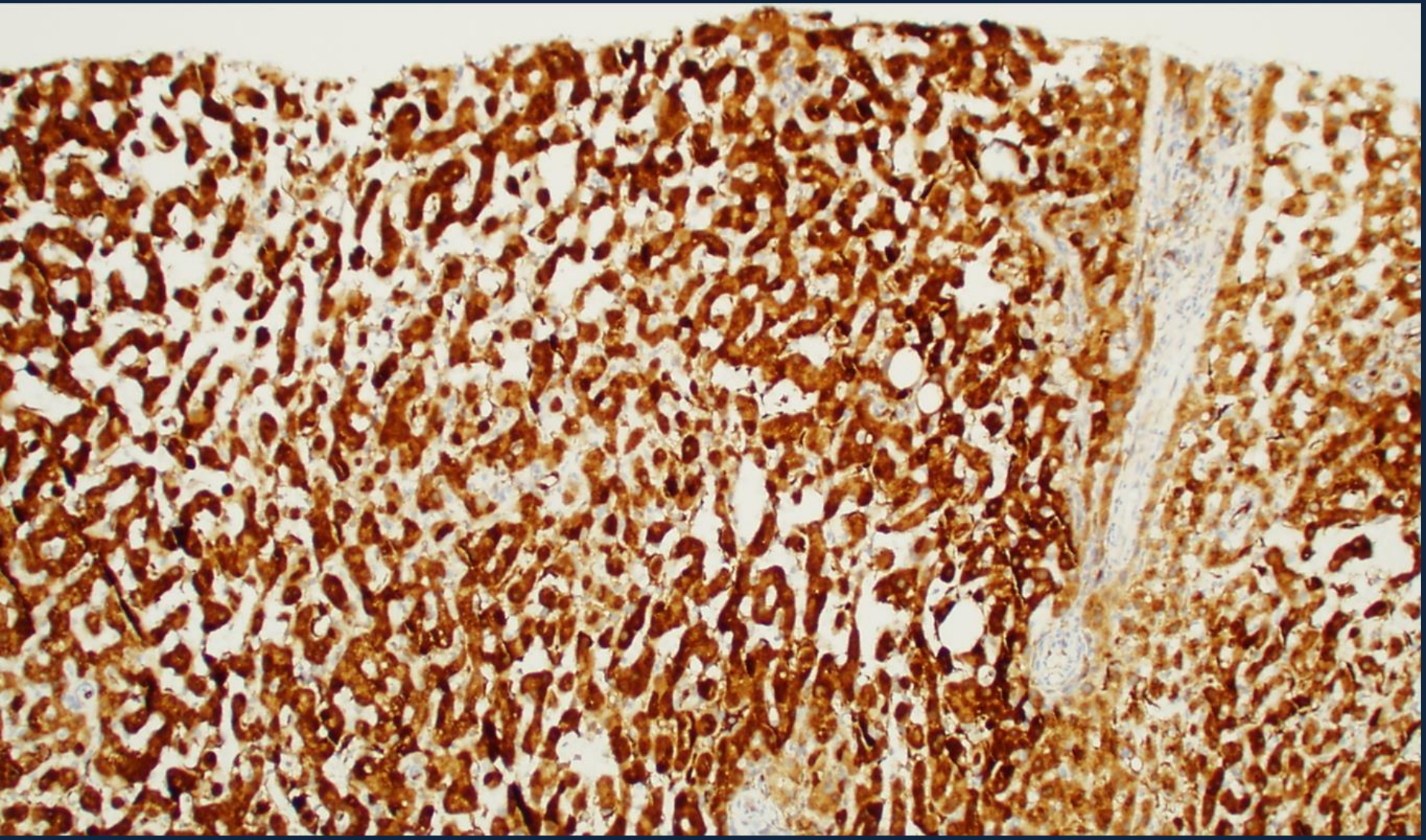




Diagnosis: Atypical hepatocellular neoplasm (AHN)

Diffuse GS: β-catenin activation

No other high risk feature



Terminology

- Atypical hepatocellular neoplasm
- Well-differentiated hepatocellular neoplasm with atypical/borderline features
- Atypical adenoma

Human Pathology

Letter to the Editor

Hum Pathol. 2014 Mar;45(3):658-60. doi: 10.1016/j.humpath.2013.09.020. Epub 2013 Nov 21.

Well-differentiated hepatocellular neoplasm of uncertain malignant potential: proposal for a new diagnostic category.

Bedossa P[1], Burt AD[2], Brunt EM[3], Callea F[4], Clouston AD[5], Dienes HP[6], Goodman ZD[7], Gouw AS[8], Hubscher SG[9], Roberts EA[10], Roskams T[11], Terracciano L[12], Tiniakos DG[13], Torbenson MS[14], Wanless IR[15].

Hum Pathol. 2014 Mar;45(3):660-1. doi: 10.1016/j.humpath.2013.09.019. Epub 2013 Nov 21.

Well-differentiated hepatocellular neoplasm of uncertain malignant potential: proposal for a new diagnostic category--reply.

Kakar S[1], Evason KJ[2], Ferrell LD[2].

Hepatocellular neoplasm with uncertain malignant potential (HUMP)

Hepatocellular neoplasm with atypical characteristics (HONC)

Are you a HUMPer or a HONCer?

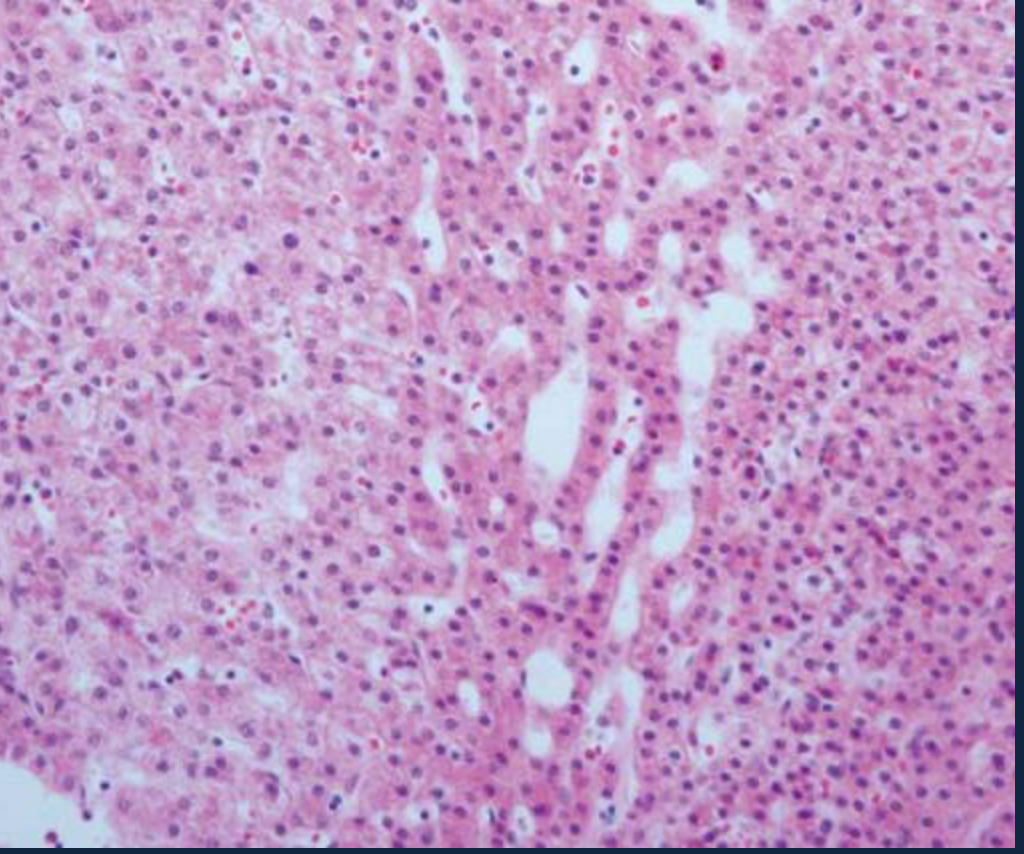
HUMP: Hepatocellular neoplasm with uncertain malignant potential
HONC: Hepatocellular neoplasm with atypical characteristics

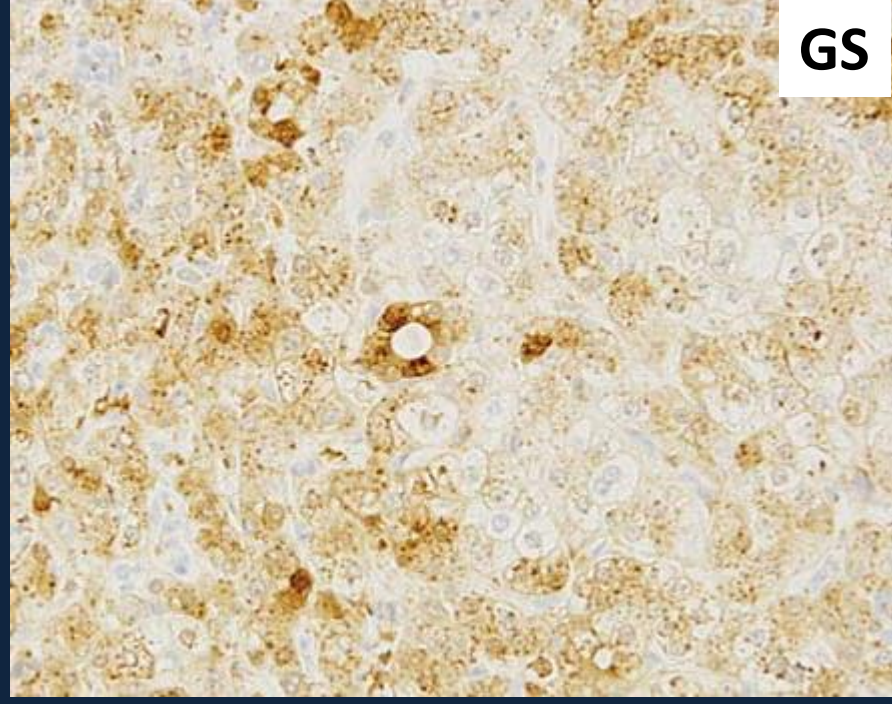
Clinical	**Male gender (any age)** **Age (>50 years)** ***Glycogen storage diseases, androgen use***
Morphologic	**Focal cytologic atypia** **Focal reticulin loss** **Nuclear β-catenin , diffuse GS**

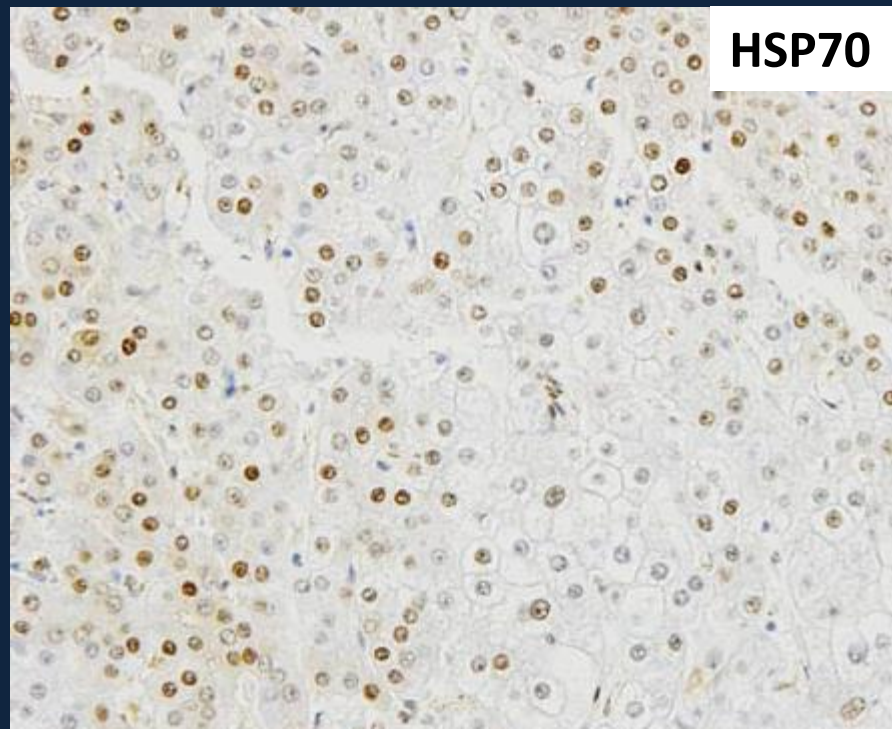
Ancillary studies

- HSP70, Glypican-3
- β-catenin mutation analysis
- TERT promoter mutation
- Cytogenetic changes: Gains of 1, 7, 8

Hale/Kakar, USCAP 2015
Pilati, Cancer Cell 2014
Evason/Kakar, Hum Pathol 2013



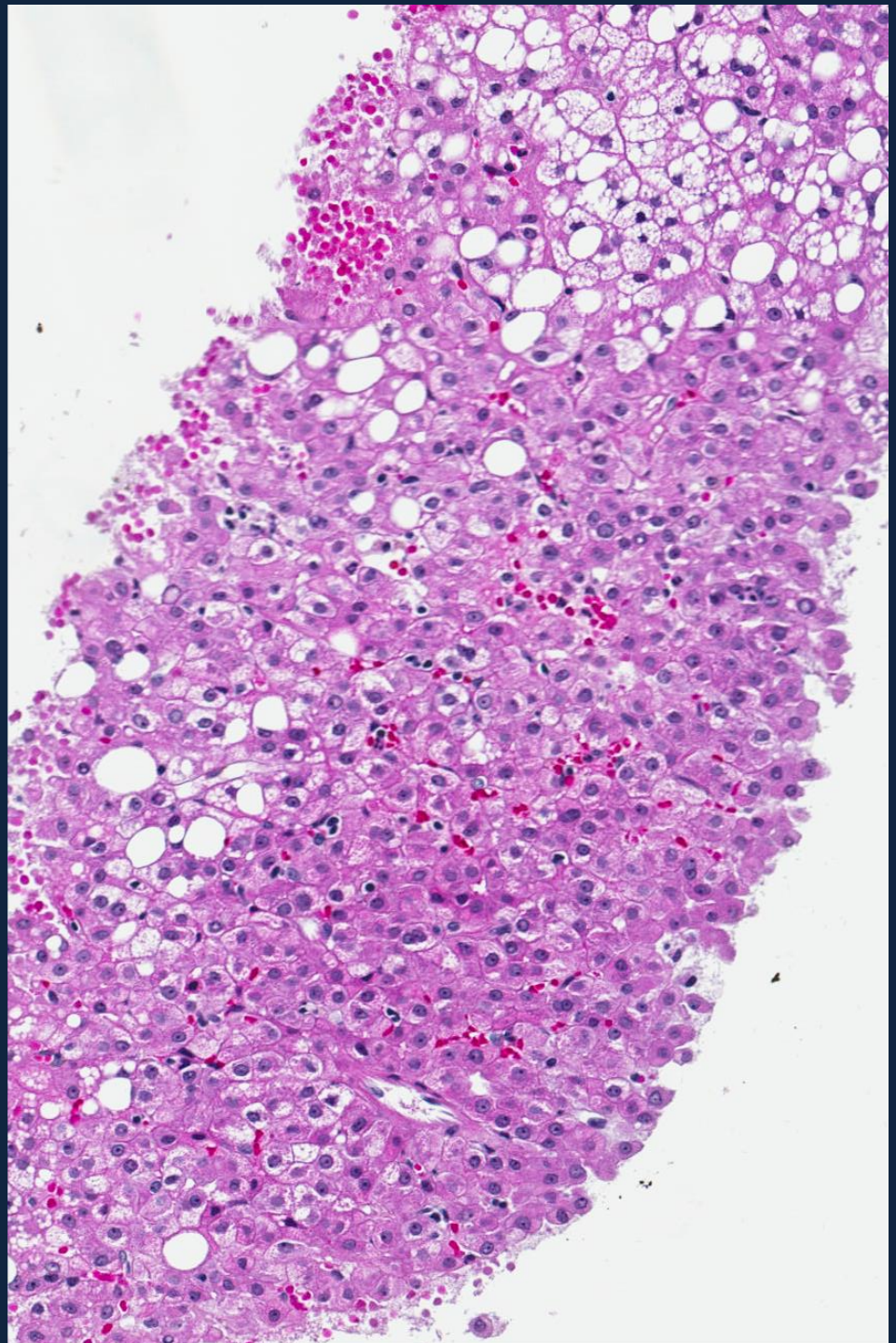
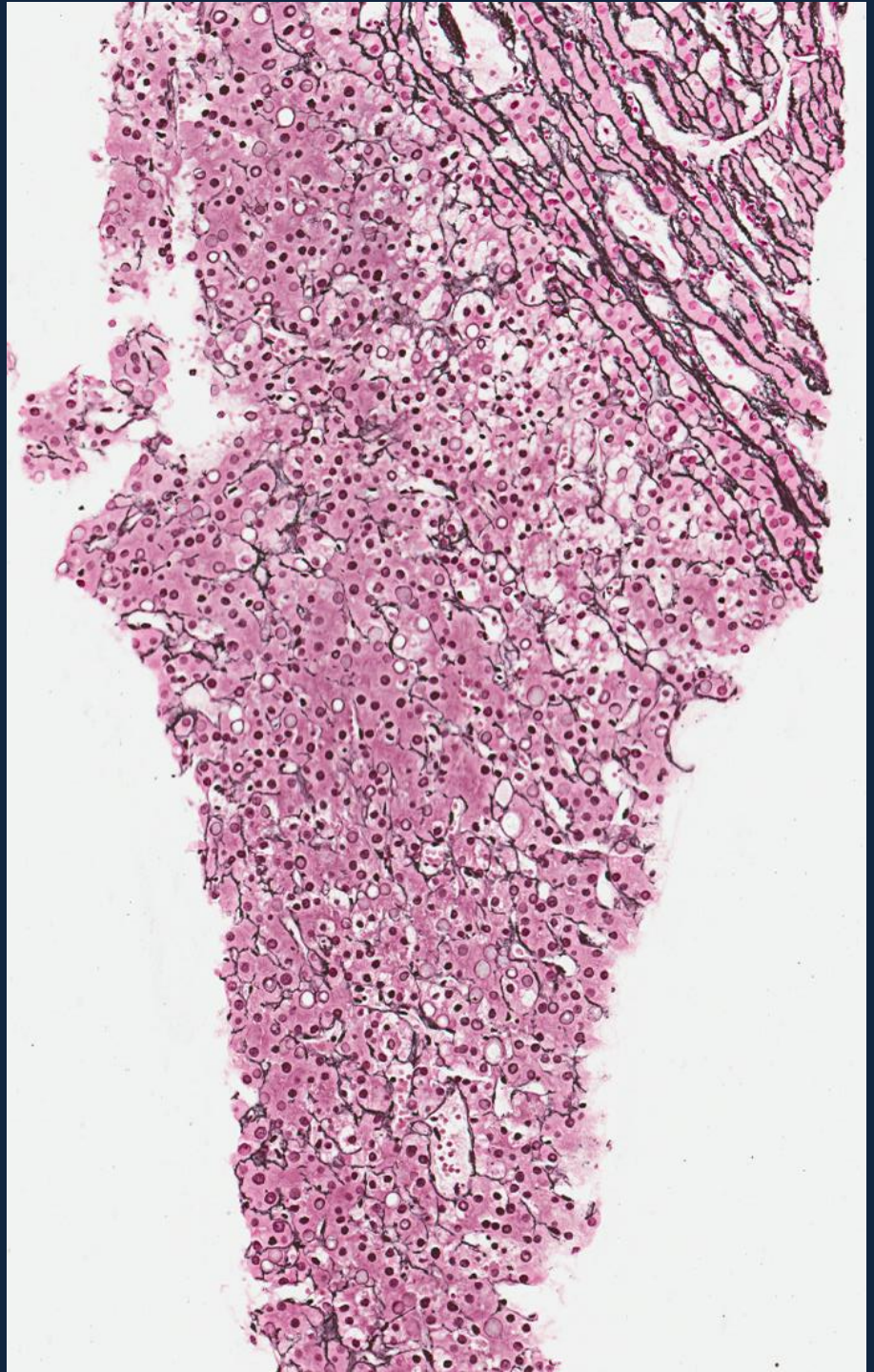




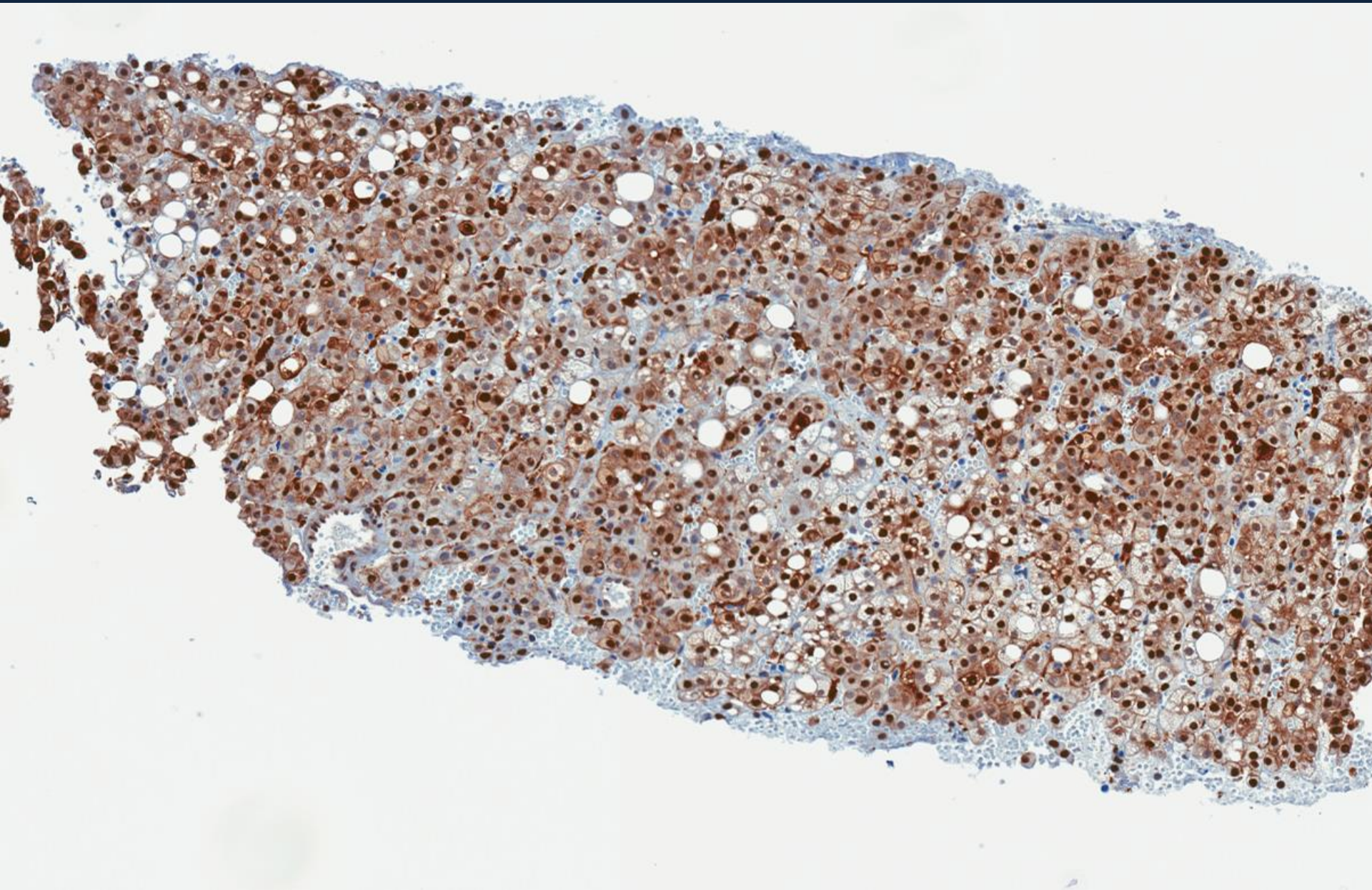
HSP70

- Maybe helpful in a small minority of atypical lesions
- Diffuse strong staining

Lagana, Appl Immunohistochem Mol Morph, 2012
Nguyen/Kakar, Mod Pathol 2015

HSP70: diffuse nuclear staining



Ancillary studies

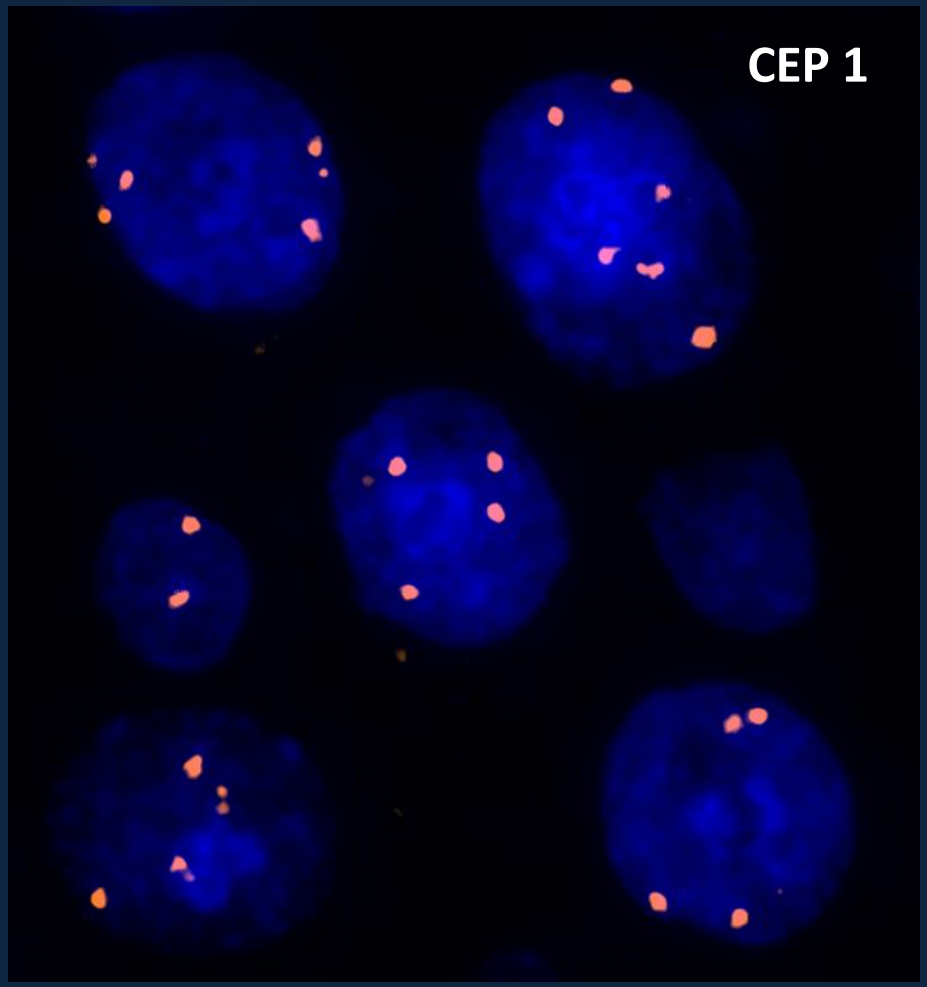
- HSP70, Glypican-3
- Sequencing:
  - β-catenin mutation: exon 3, others (exon 7,8)
  - *APC, AXIN* mutations
- TERT promoter mutation
- Cytogenetic changes: Gains of 1, 7, 8

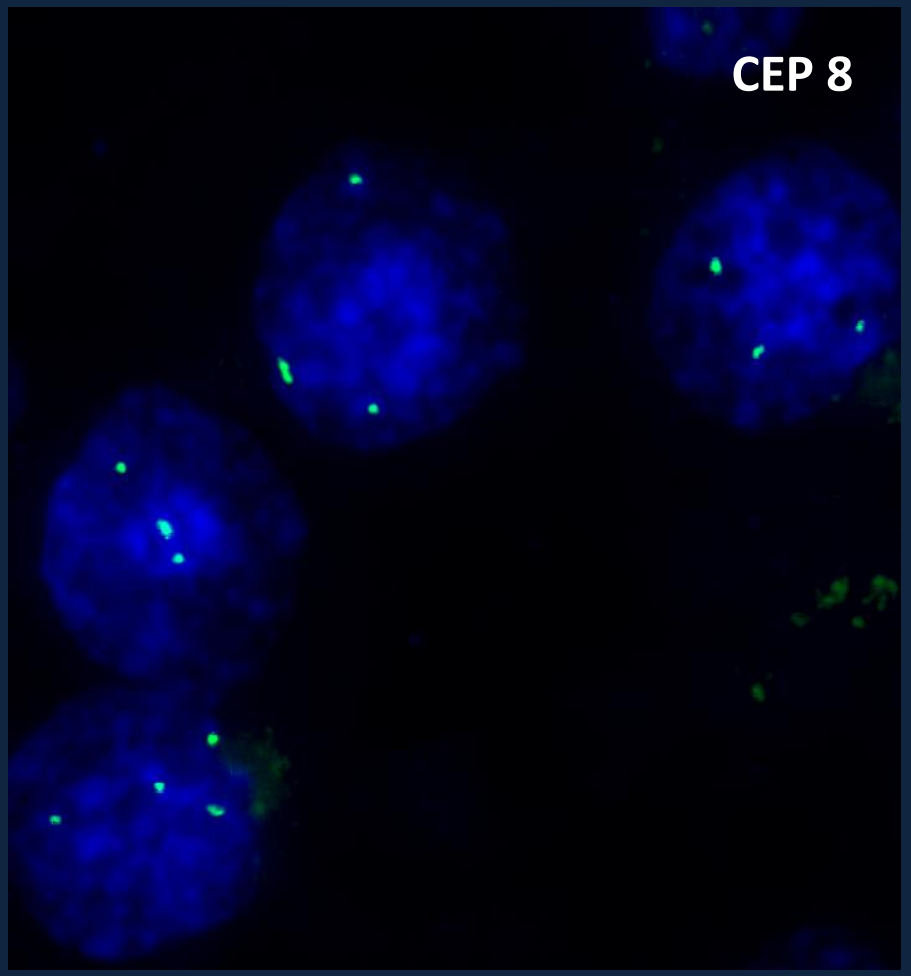
Hale/Kakar, USCAP 2015
Pilati, Cancer Cell 2014
Evason/Kakar, Hum Pathol 2013

Atypical hepatocellular adenoma–like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas☆,☆☆

Kimberley J. Evason MD, PhD[a], James P. Grenert MD, PhD[a], Linda D. Ferrell MD[a], Sanjay Kakar MD[a,b,*]

Human Pathology (2013) 44, 750–758





FISH by JP Grenert, UCSF

Recommendations

No map-like GS typical of FNH
Cytoarchitectural atypia not enough for HCC

Biopsy	Diagnosis
-Woman **-No high risk feature**	Hepatocellular adenoma
High risk features **-Man (any age)** **-Age >50 years** **-Focal atypical features insufficient for HCC** **-β-catenin activation**	Atypical hepatocellular neoplasm (AHN) -Reason for AHN can be stated in a comment -Other terms like HUMP

Recommendations

No map-like GS typical of FNH
Cytoarchitectural atypia not enough for HCC

Resection	Diagnosis
-Woman **-No high risk feature**	Hepatocellular adenoma
-Man (any age) **-Age >50 years** **-No other risk factor**	Hepatocellular adenoma (can recommend follow-up, as HCA are uncommon in this setting)
Focal atypical features insufficient for HCC	HCA or AHN Depends on extent of atypia on resection
β-catenin activation	β-catenin HCA (WHO 2010), or AHN with β-catenin activation

Recommendations

HCC

- **Cytoarchitectural abnormalities**
- **Multifocal reticulin loss**
- **Do not use AHN in this setting**

Management of HCA

Management	Tumor characteristics
Conservative with annual surveillance	Solitary HCA, <5 cm No high risk features
Resection	Women: solitary HCA ≥5 cm Men (?women>50 years): all cases High-risk features

IHC: subtyping adenoma

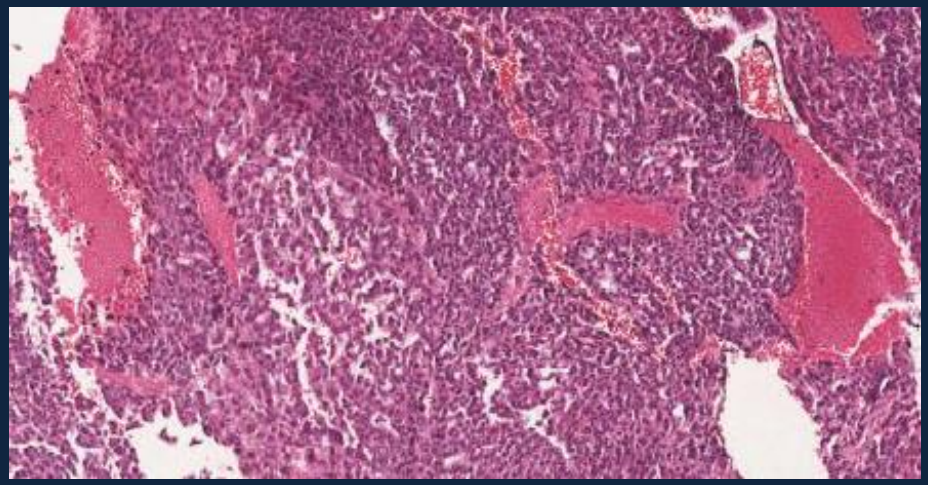
- Subtyping adenoma not necessary if β-catenin activation excluded
- Establish diagnosis of adenoma based on morphology, not by IHC used for subtyping
- Pitfalls

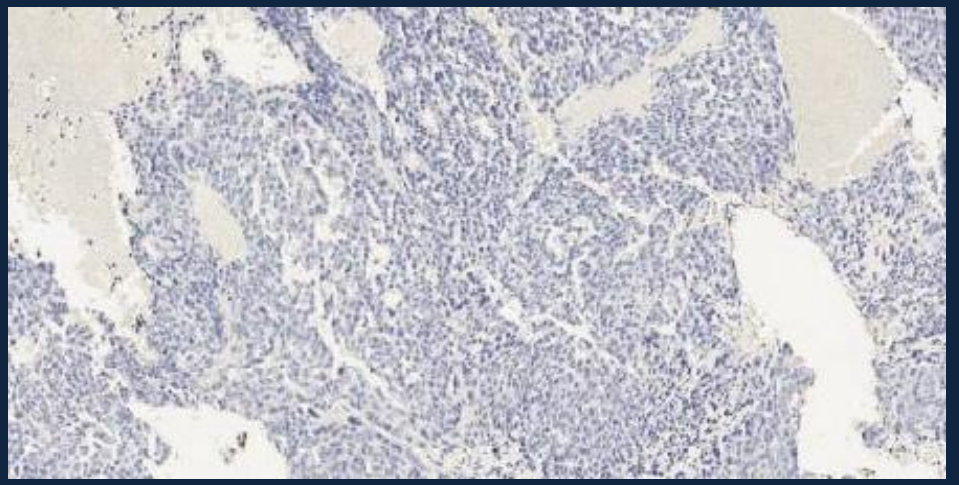
  -LFABP loss can occur in HCC

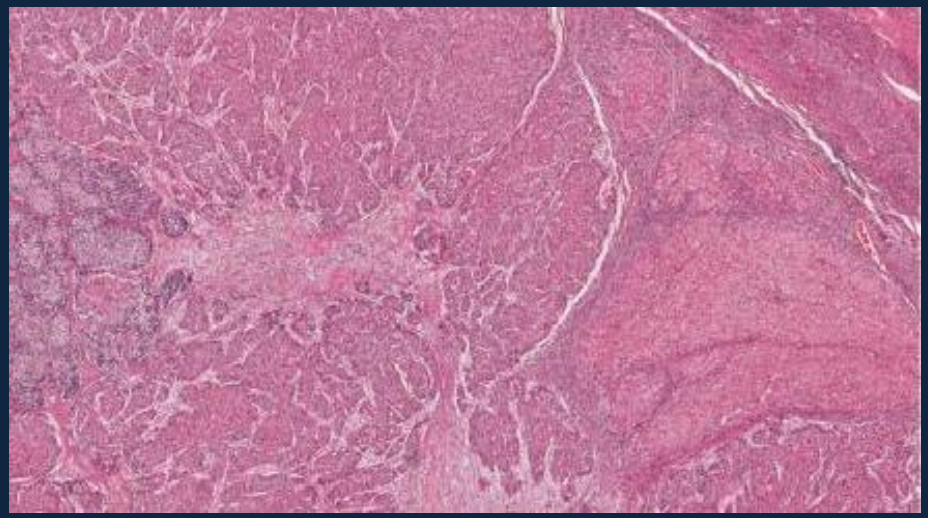
  -SAA, CRP staining can be seen in HCC

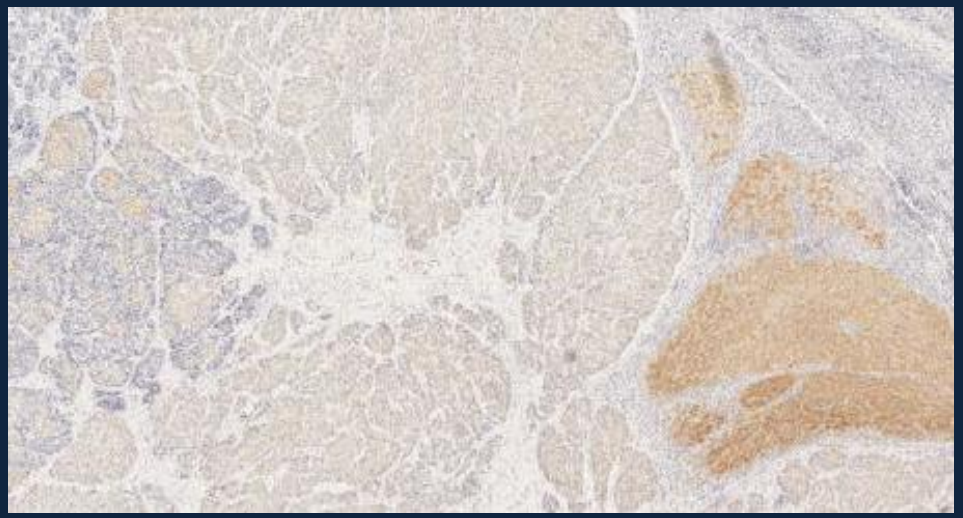
  -Diffuse GS staining in HCC

LFABP loss in HCC







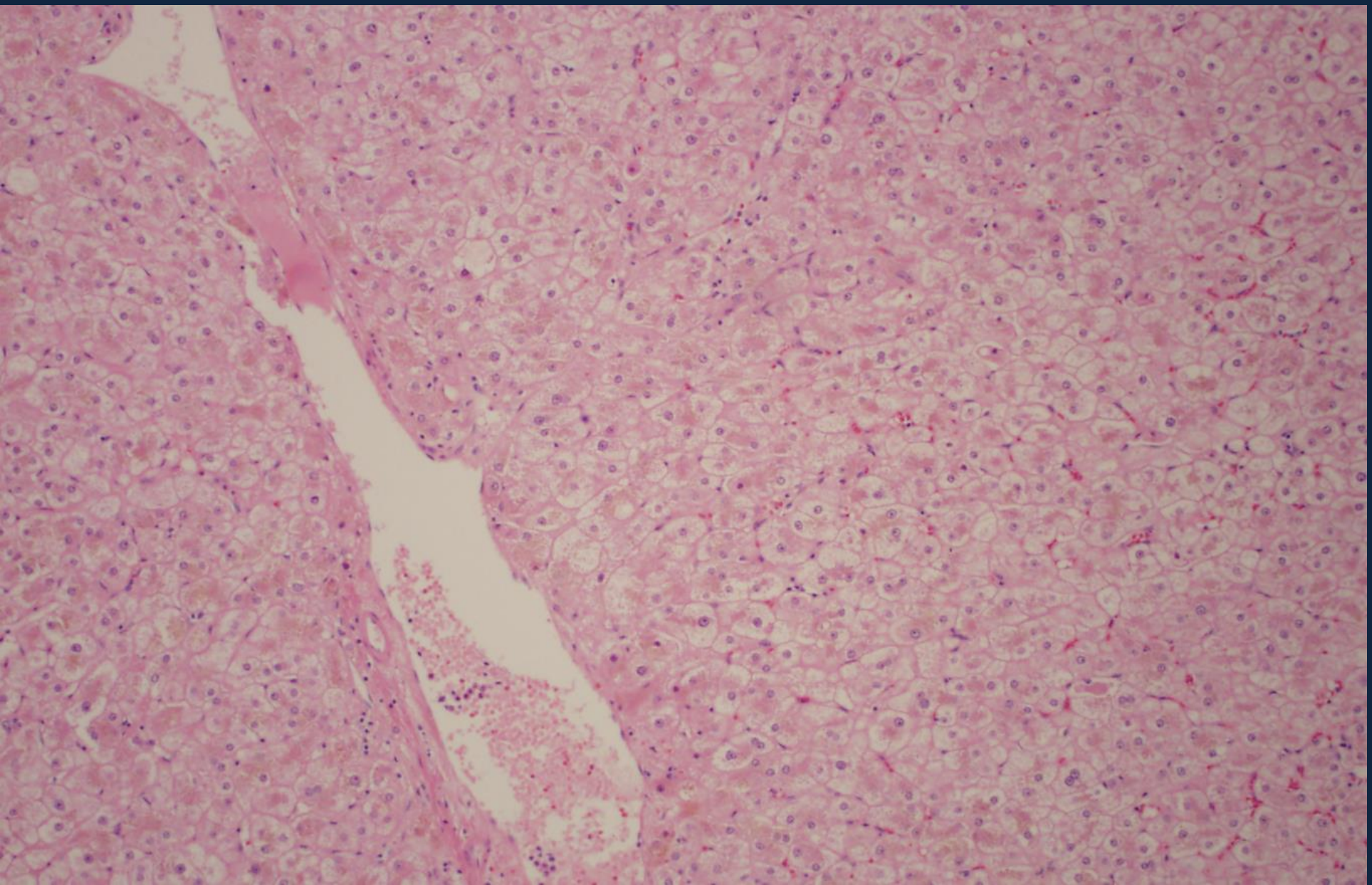


Cho/Gill, Hum Pathol 2016

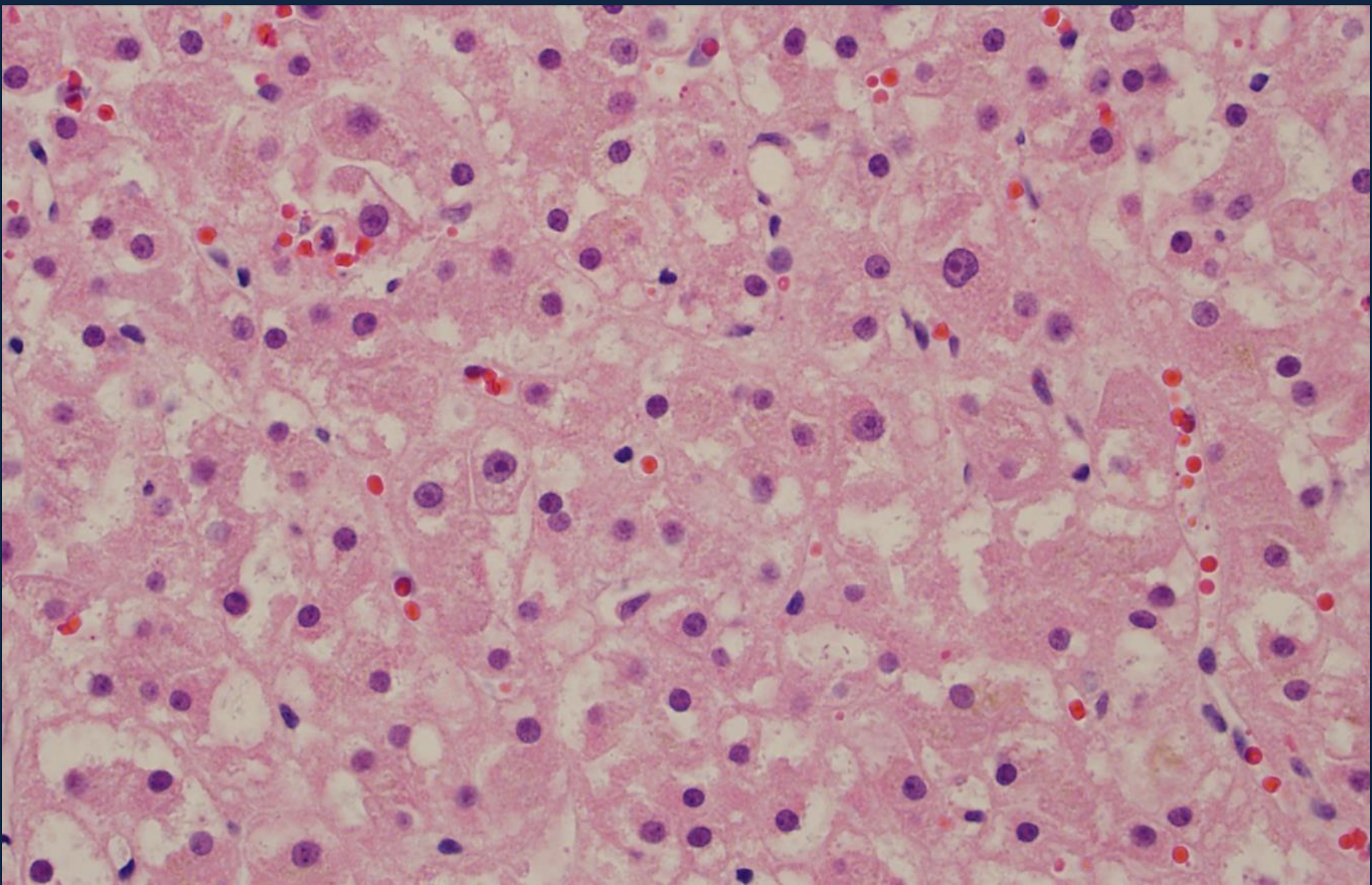
Hepatic adenomatosis

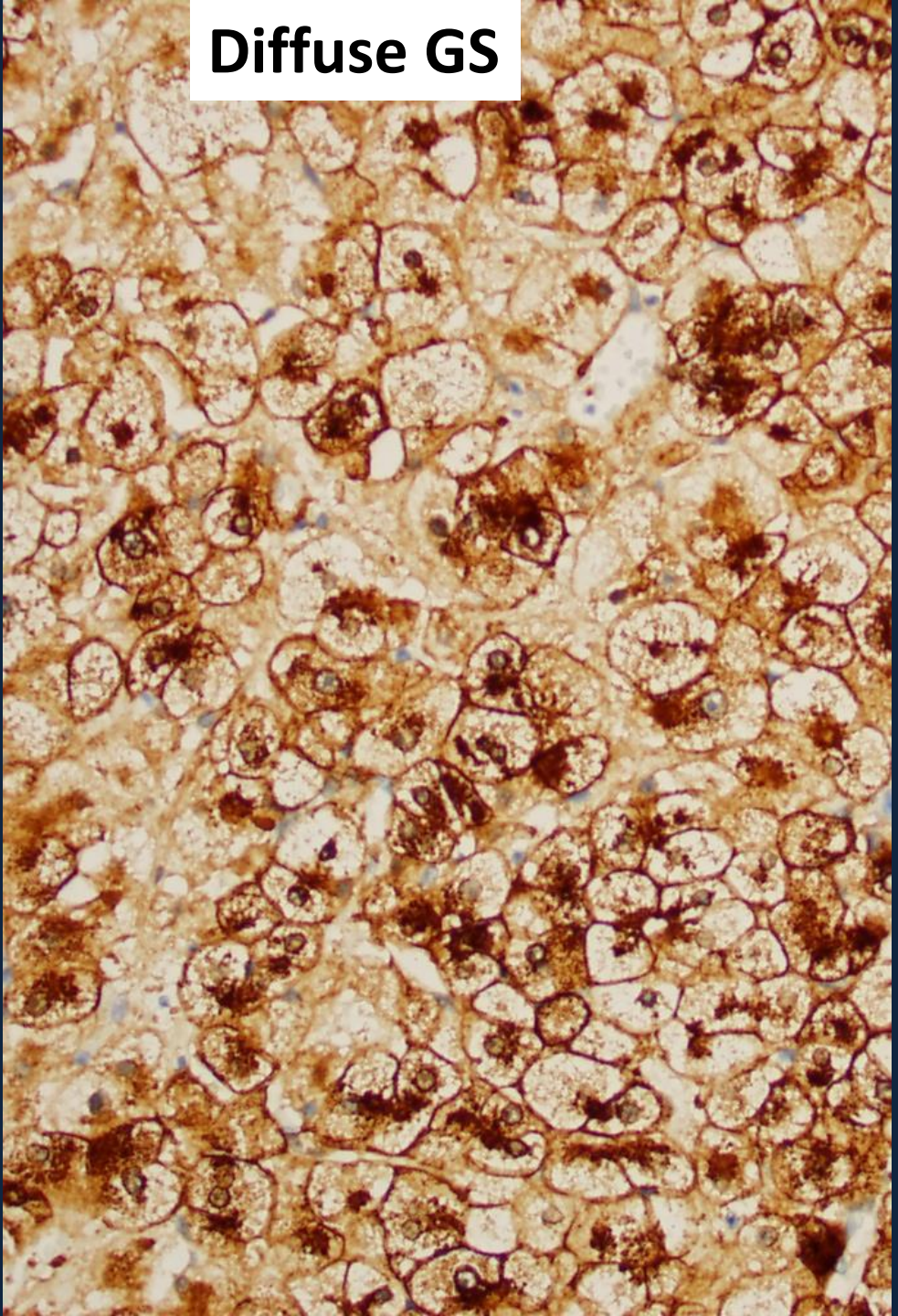
- By definition, ≥10 adenomas
- Young women
- Most are HNF1α-inactivated or inflammatory
- Pathogenesis
  - Obesity, less strong association with OCs
  - Germline *HNF1α* mutations
- Glycogen storage disease type I, III

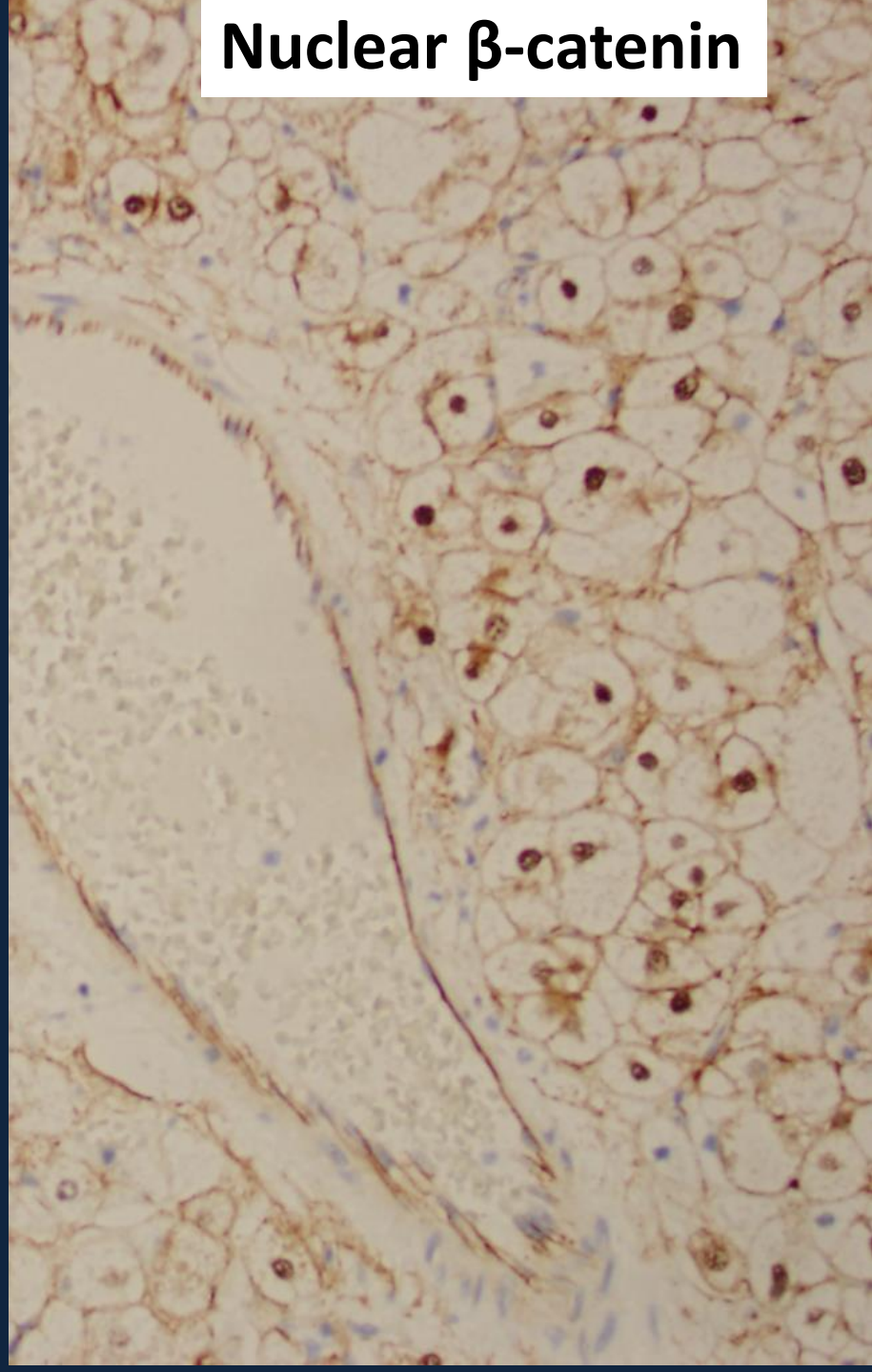
34/M, 4.5 cm liver mass



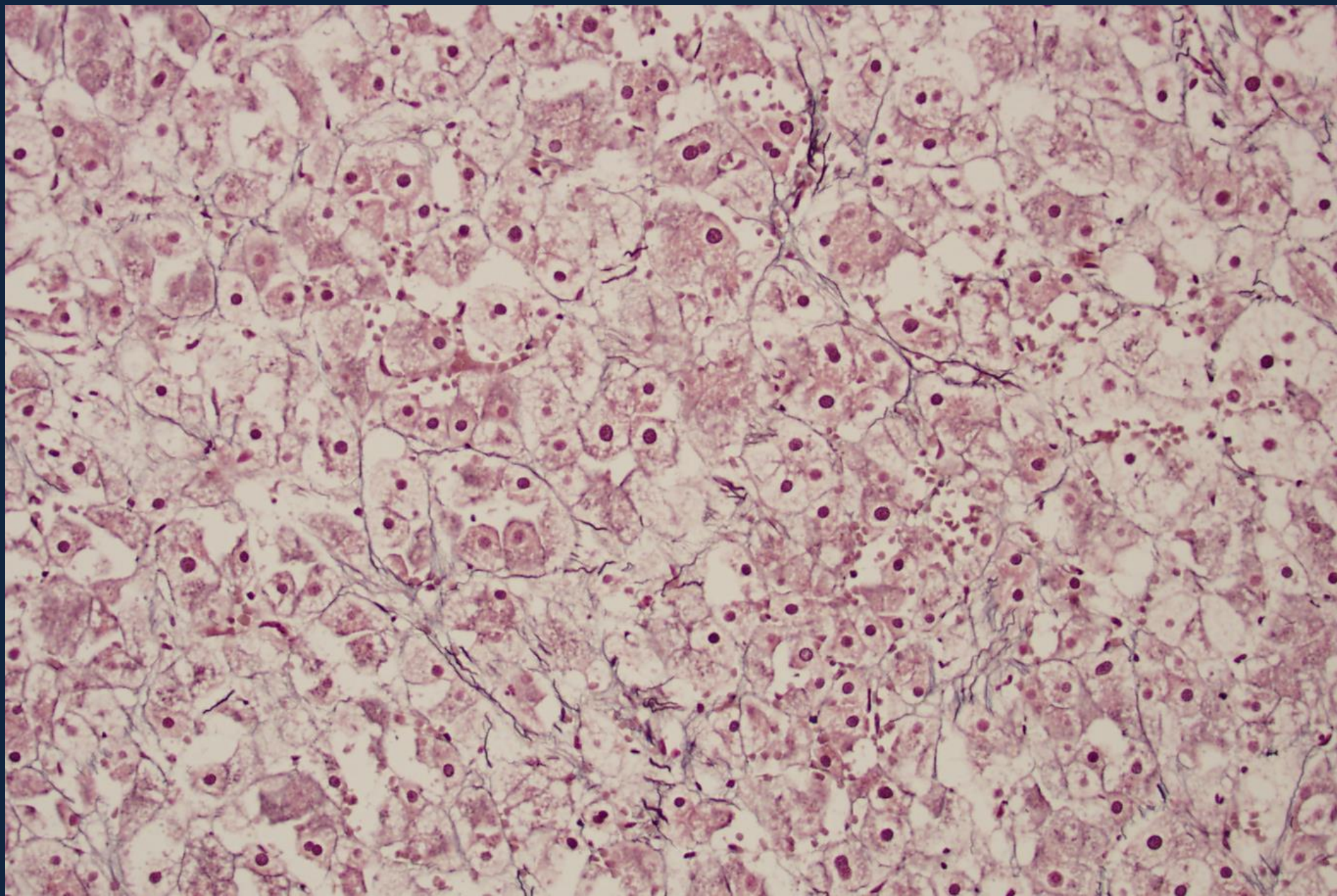
Minimal atypia




Diffuse GS


Nuclear β-catenin

Reticulin loss



Atypical features

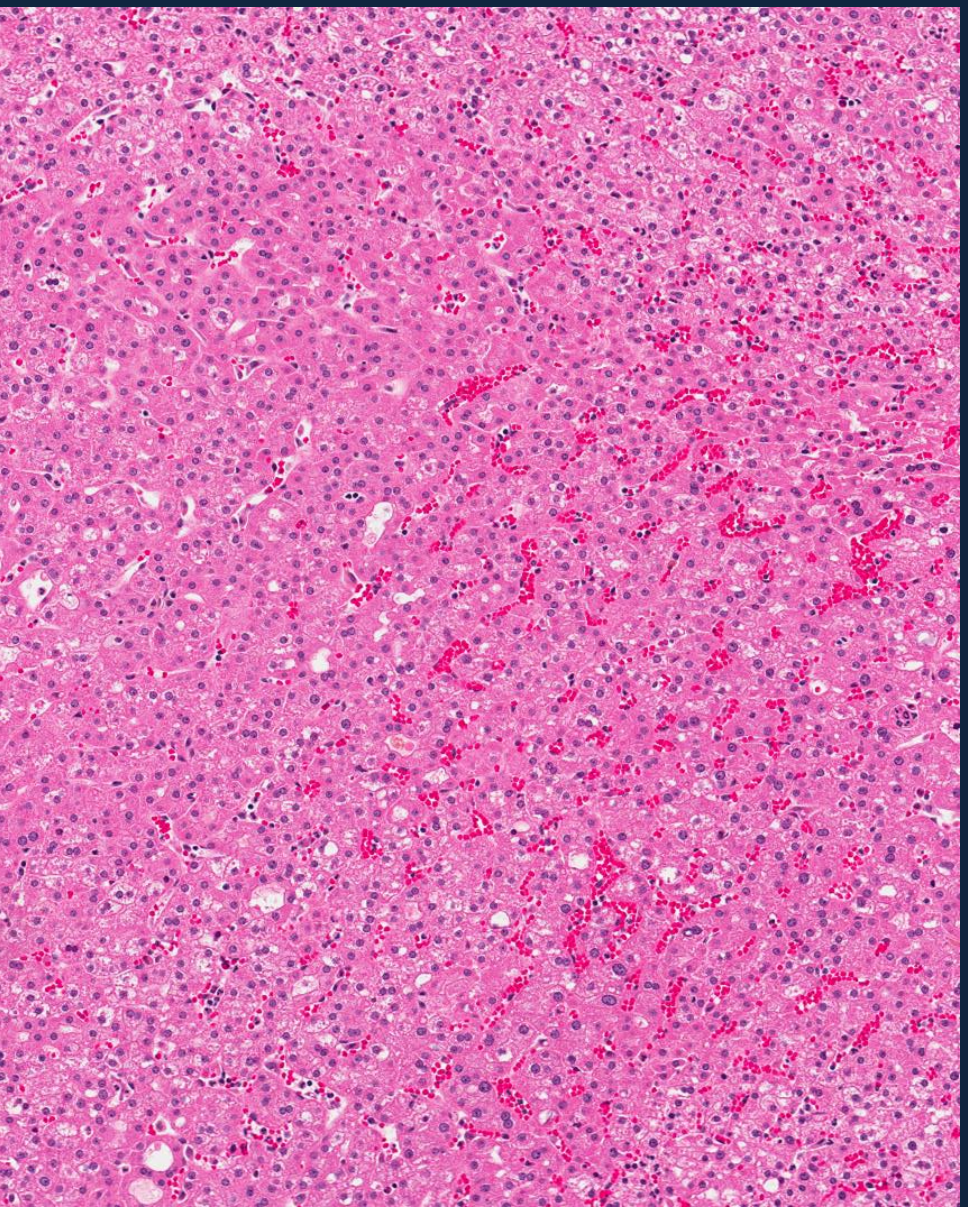
- Cytoarchitetural abnormalities
- Extensive loss of reticulin

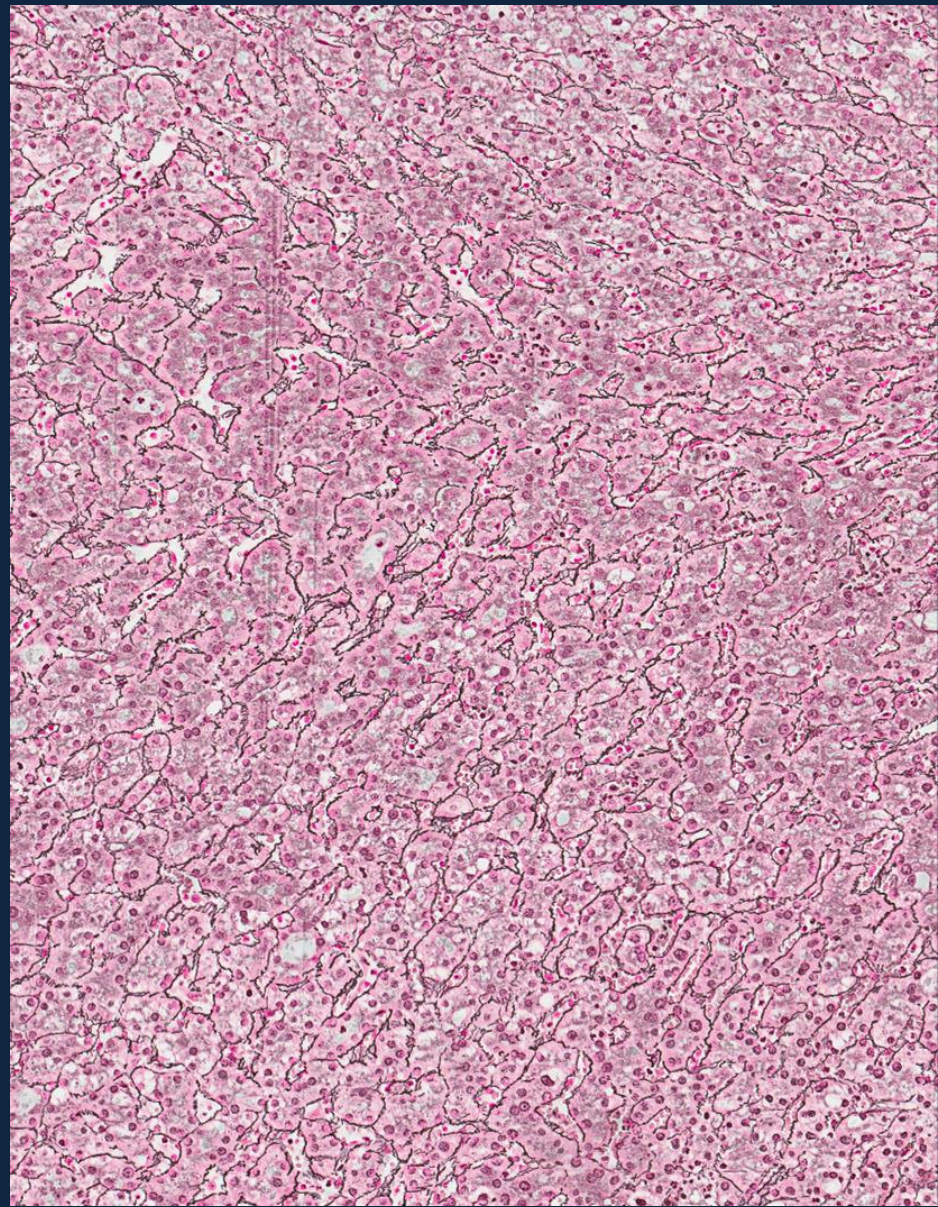
Atypical hepatocellular neoplasm, or HCC

Summary

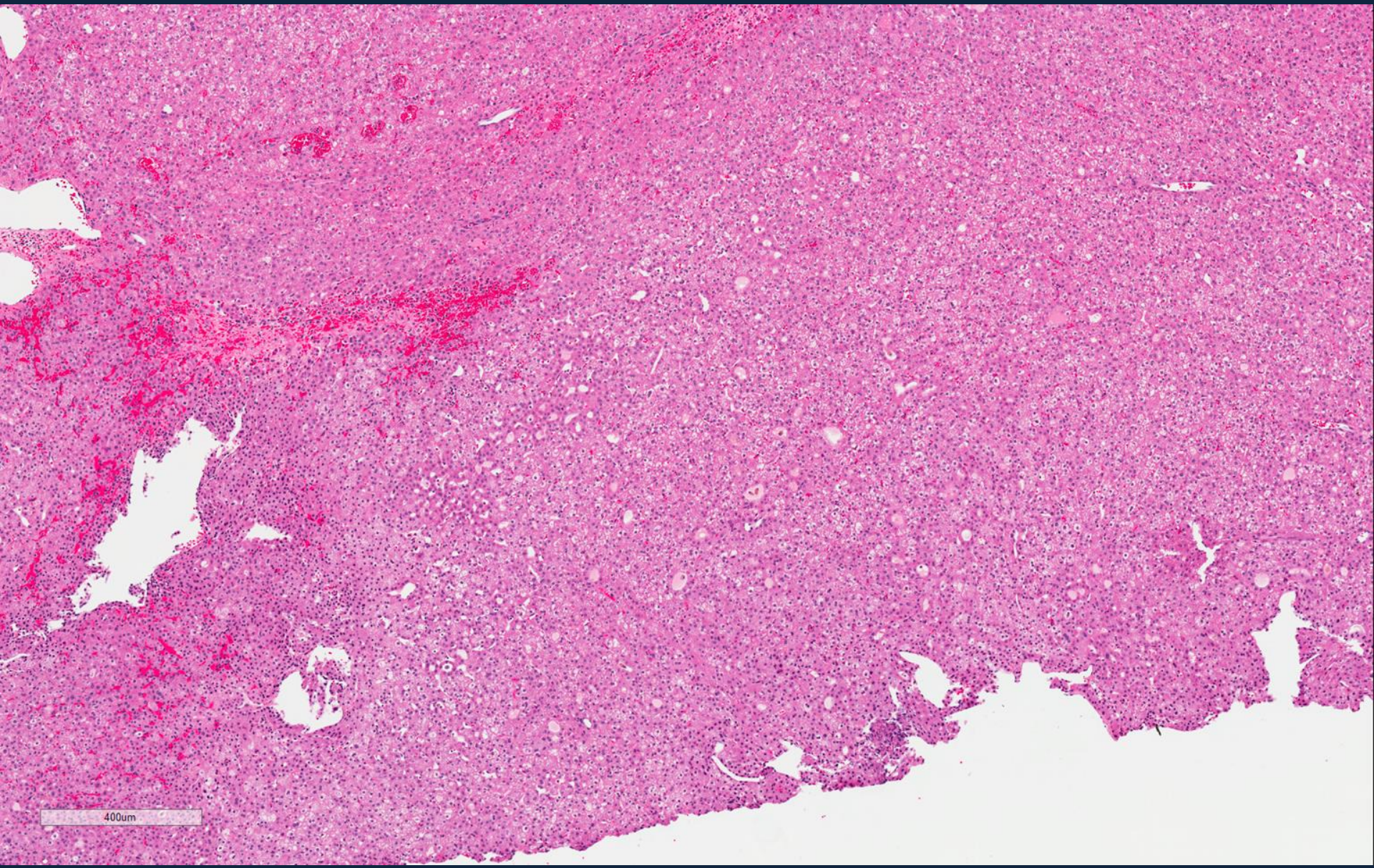
Biopsy diagnosis	Implication
FNH vs HCA	Resection vs no resection Minimum stains: GS, SAA
Hepatocellular tumors Men, size ≥5 cm FNH excluded	Resection recommended -Risk of bleeding -Risk of HCC Distinction between HCA, AHN and HCC on bx may not be important
Hepatocellular tumors Woman, size <5 cm FNH excluded	HCA vs AHN/HCC necessary Multiple: dictated by size of largest nodule

40/F, 9 cm liver mass
Most of the tumor: no atypia

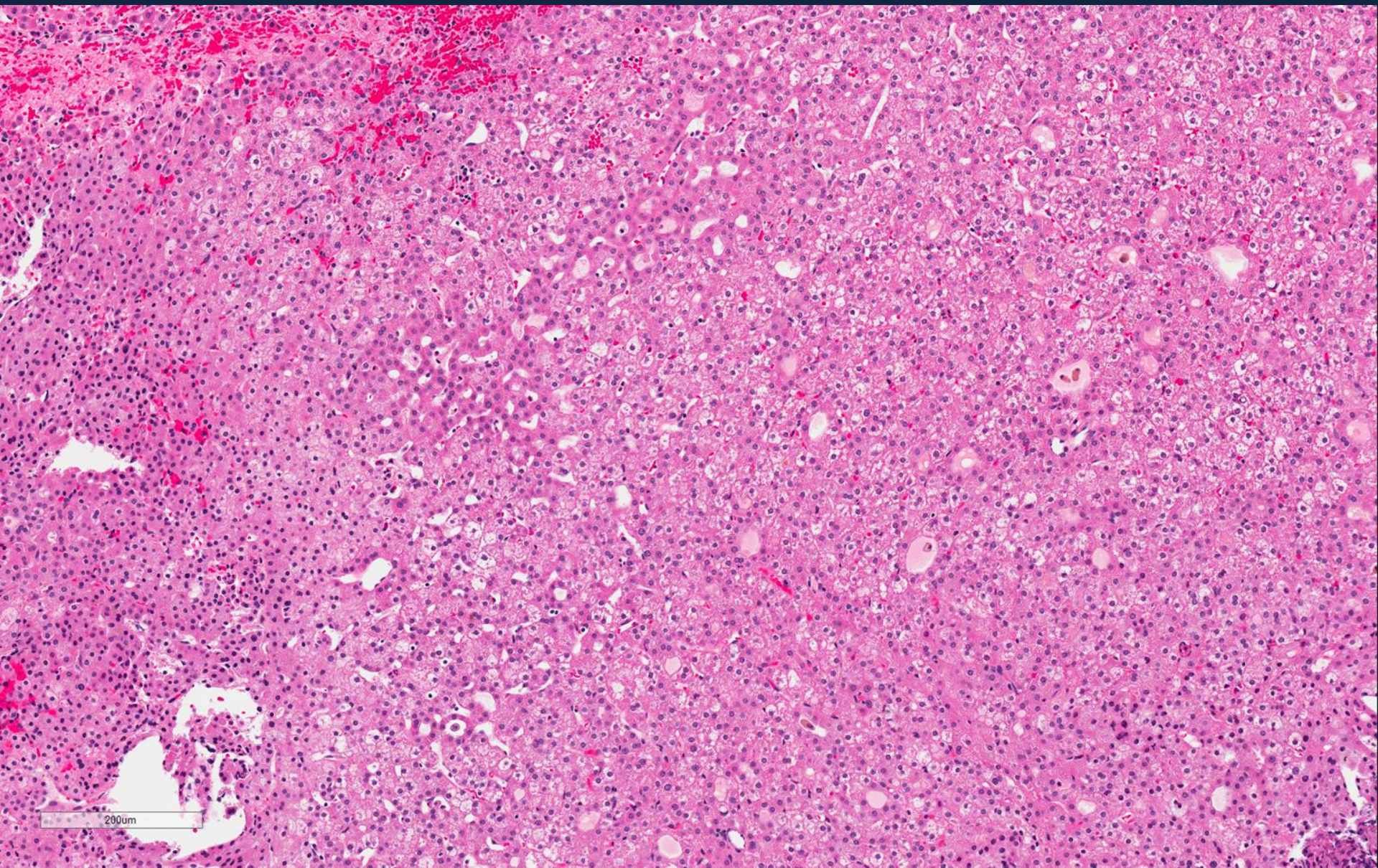




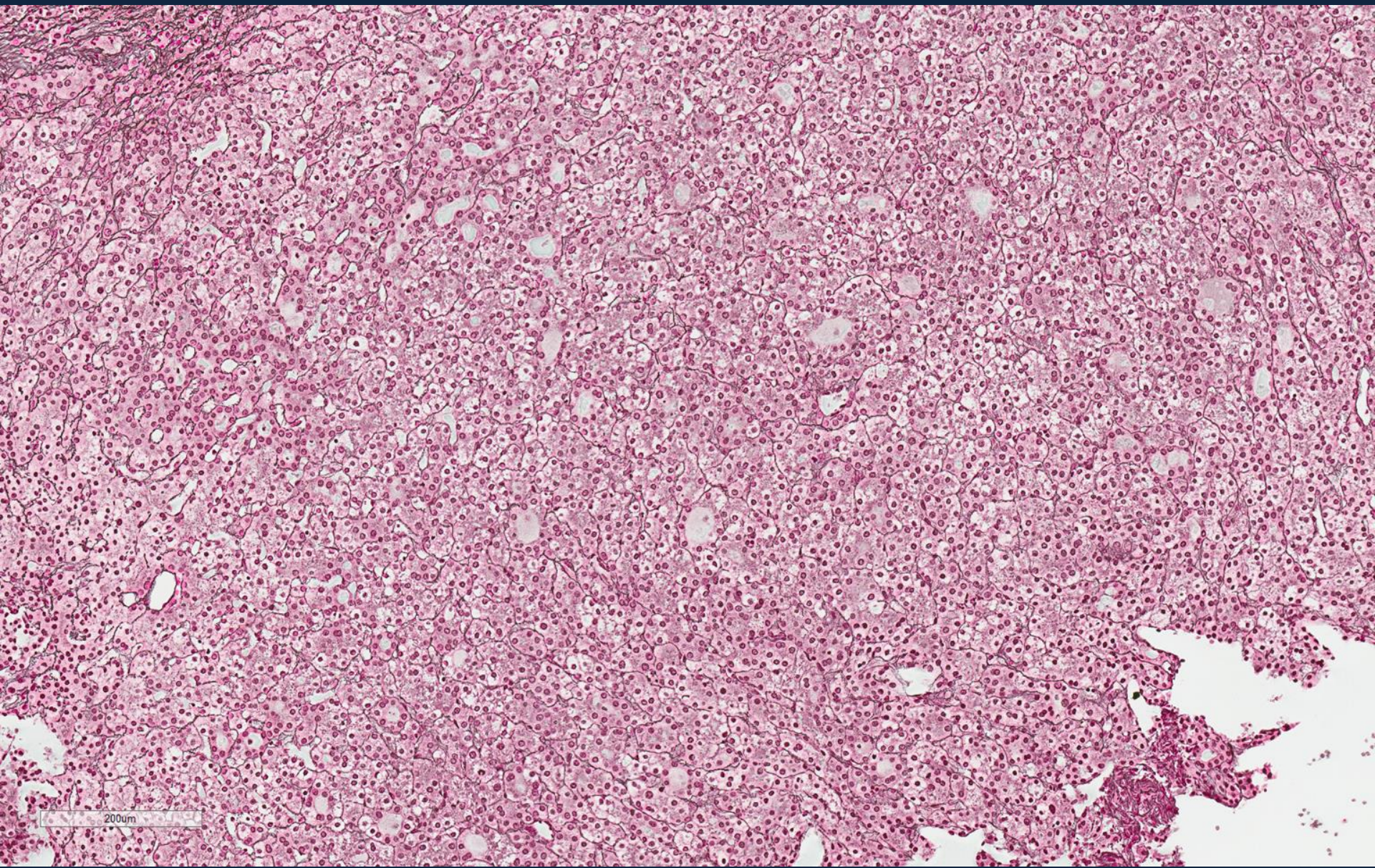
8 mm atypical focus



Pseudoacinar, small cell change



Reticulin stain



Atypical features

- Cytoarchitetural abnormalities
- Abnormal reticulin pattern

Atypical hepatocellular neoplasm, or HCC arising in HCA

Summary

Biopsy diagnosis	Implication
FNH vs HCA	Resection vs no resection Minimum stains: GS, SAA
Hepatocellular tumors Men, size ≥5 cm FNH excluded	Resection recommended -Risk of bleeding -Risk of HCC Distinction between HCA, AHN and HCC on bx may not be important
Hepatocellular tumors Woman, size <5 cm FNH excluded	HCA vs AHN/HCC necessary Multiple: dictated by size of largest nodule

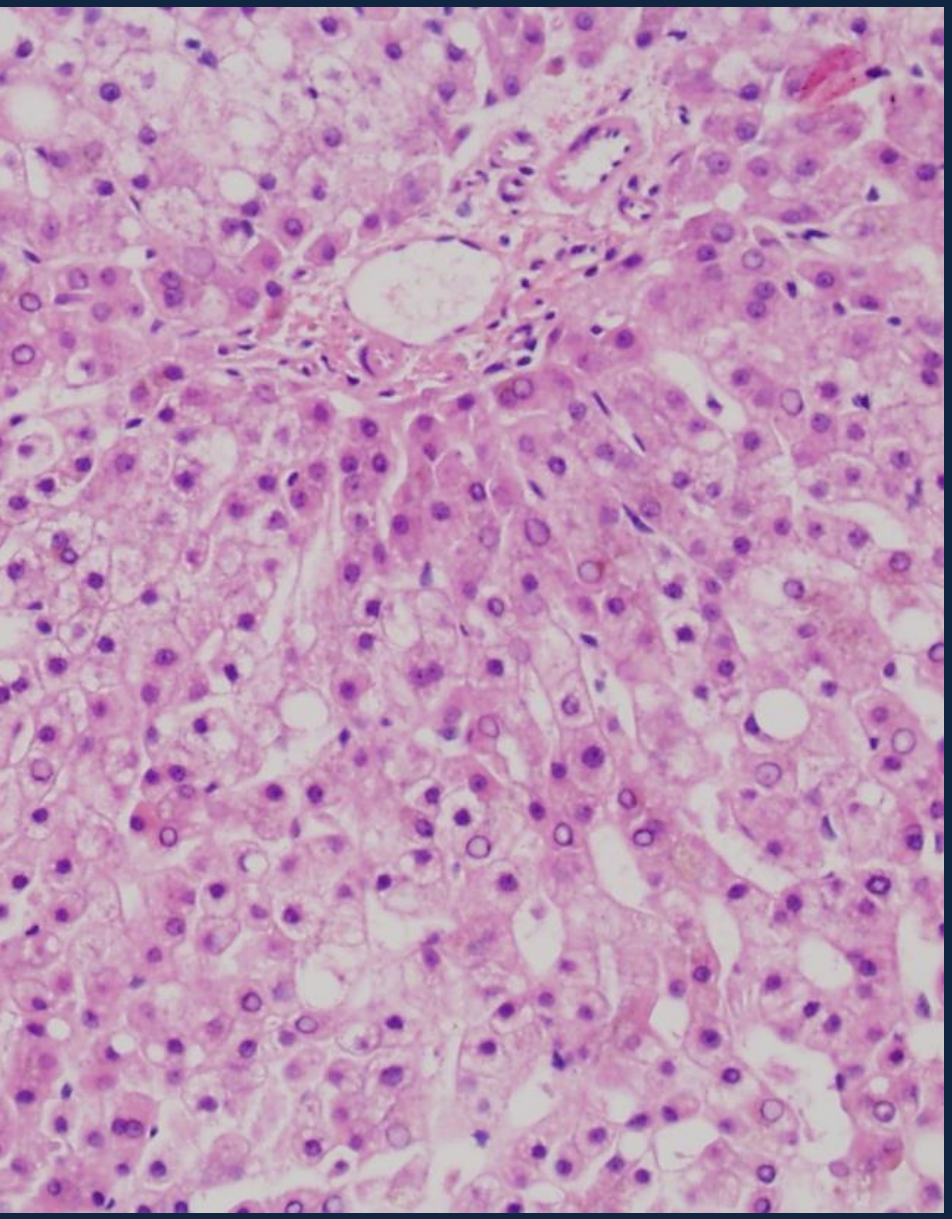
Minimum stains

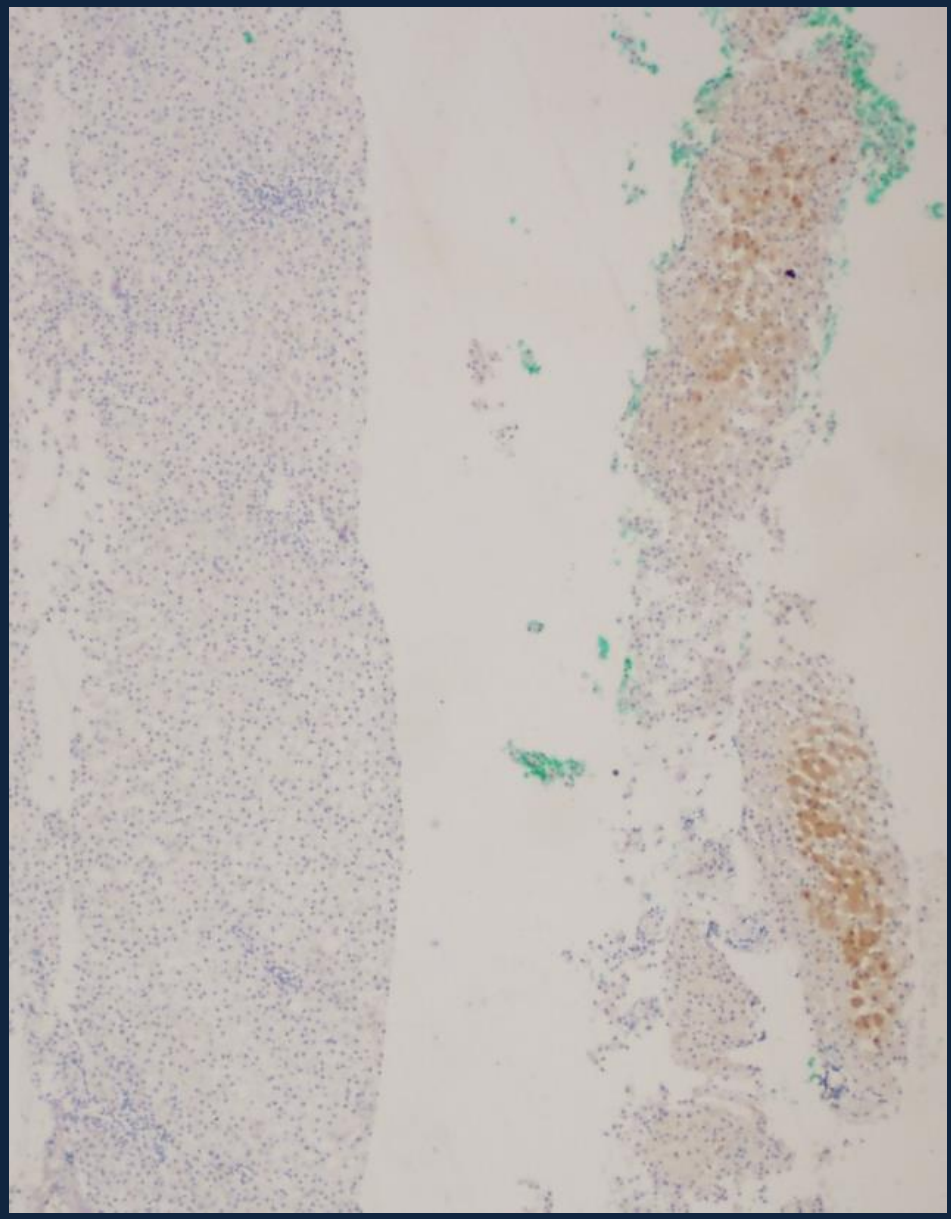
Stain	Interpretation
Reticulin	Loss: HCC
GS	Diffuse: Suggest β-catenin activation Map-like: FNH Patchy, no specific pattern: HCA
SAA	Inflammatory HCA

H-HCA: diagnostic challenges

Diagnostic challenge	Approach
Fat may be absent	Overall morphologic features LFABP, other stains
Fat in other HCA subtypes, FNH	Overall morphologic features LFABP, other stains
LFABP can be weak	Titrate stain appropriately 'All or none': any +ve staining usually means LFABP retained
LFABP loss in HCC	LFABP is used to subtype HCA Should not be used to diagnose HCA

H-HCA without fat





Unclear situations

Small (<5 cm) tumors

- Atypical clinical setting, no atypical morphologic features
- Borderline GS staining pattern

Atypical neoplasm extending to margin

Management of HCA

Management	Tumor characteristics
Conservative with annual surveillance	Solitary HCA <5 cm
Resection	Women: solitary HCA ≥5 cm Men (?women>50 years): all cases High-risk features

HCA subtypes: US and Europe

Subtype	Bioulac-Sage, Hepatol, 2007 (n=93)	Shafizadeh/Kakar Hum Path 2014 (n=28)	Thung, EASL 2013 (n=61)	Bioulac-Sage, AJSP 2012 (n=137)
HNF1α	33%	29%	33%	22%
Inflammatory	40%	32%	44%	53%
β-catenin, not IHCA	17%	0	2%	2%
IHCA with β-catenin	2%	3%	2%	11%
Unclassified	8%	36%	16%	13%

Shafizadeh/Kakar, Hum Pathol 2014

Imaging features

	FNH	Inflammatory HCA
Central scar	Present	Absent
Contrast CT enhancement	Early homogenous	Heterogeneous and persistent
MRI TI-weighted	Hypointense	Hyperintensity
MRI T2-weighted	Hypointense	Strong hyperintensity

I-HCA: diagnostic challenges

Diagnostic Challenge	Approach
Typical morphology not seen	10%, SAA and/or CRP positive
Morphology like I-HCA, SAA negative	SAA negative in 5-10% Most are CRP-positive
CRP specificity is low FNH often positive in periseptal region	Overall morphologic features Other stains: SAA, GS
SAA, CRP positive in adjacent liver	**Focus on morphology** **Obtain CD34 stain**
I-HCA with diffuse GS staining	10% of cases Considered as high-risk HCA
Overlap with FNH	Morphology SAA, CRP, GS

I-HCA: diagnostic challenges

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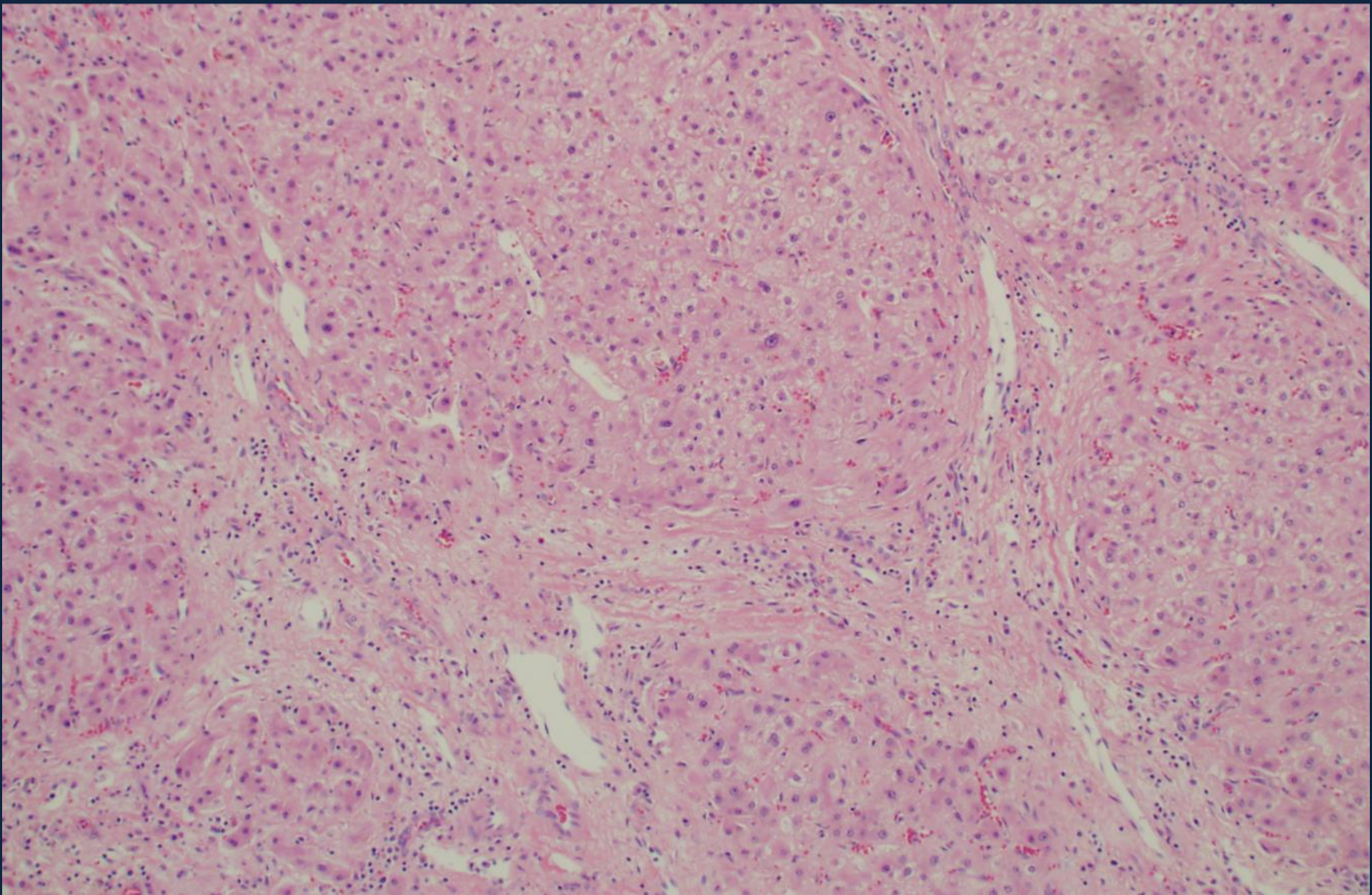
SAA, CRP positive in adjacent liver	Focus on morphology Obtain CD34 stain
I-HCA with diffuse GS staining	**10% of cases** **Considered as high-risk HCA**
Overlap with FNH	Morphology SAA, CRP, GS

HCC: criteria for diagnosis

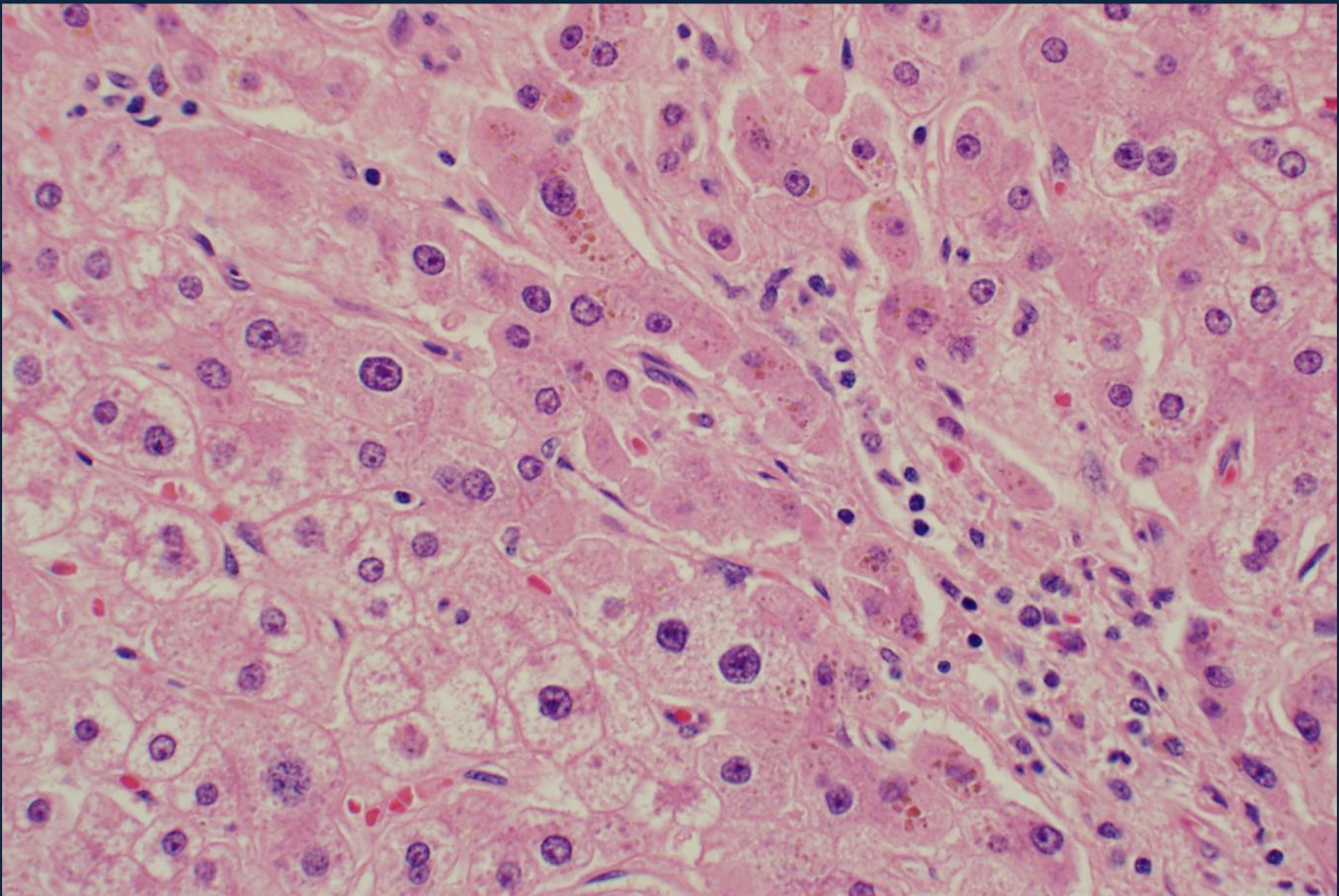
Two criteria

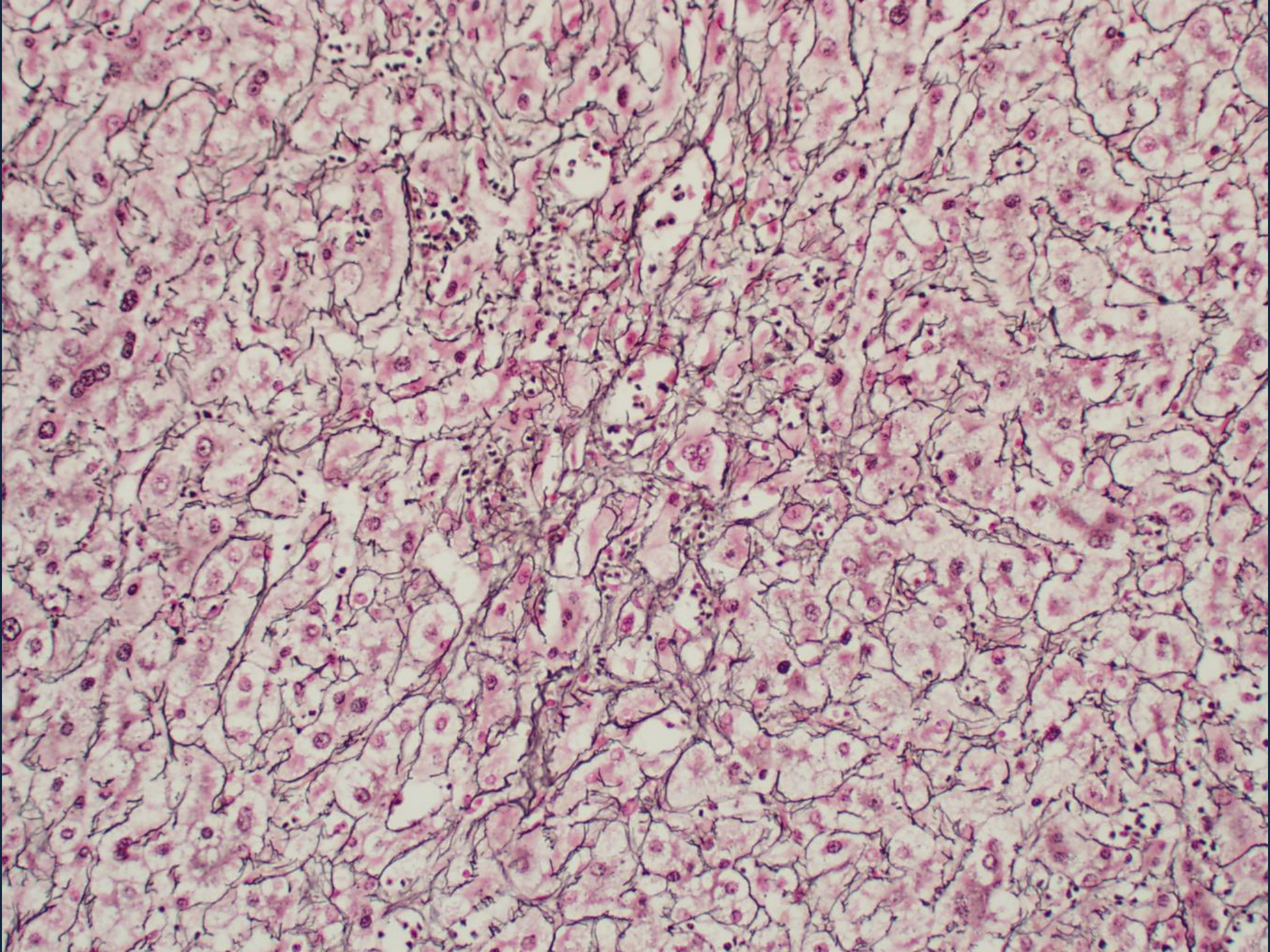
- **Cytoarchitectural abnormalities**
  - **Small cell change/cytologic atypia**
  - **Thick cell plates**
  - **Prominent pseudoacinar architecture**
- **Multifocal reticulin loss**
  (not necessary if sufficient cytoarchitectural atypia)

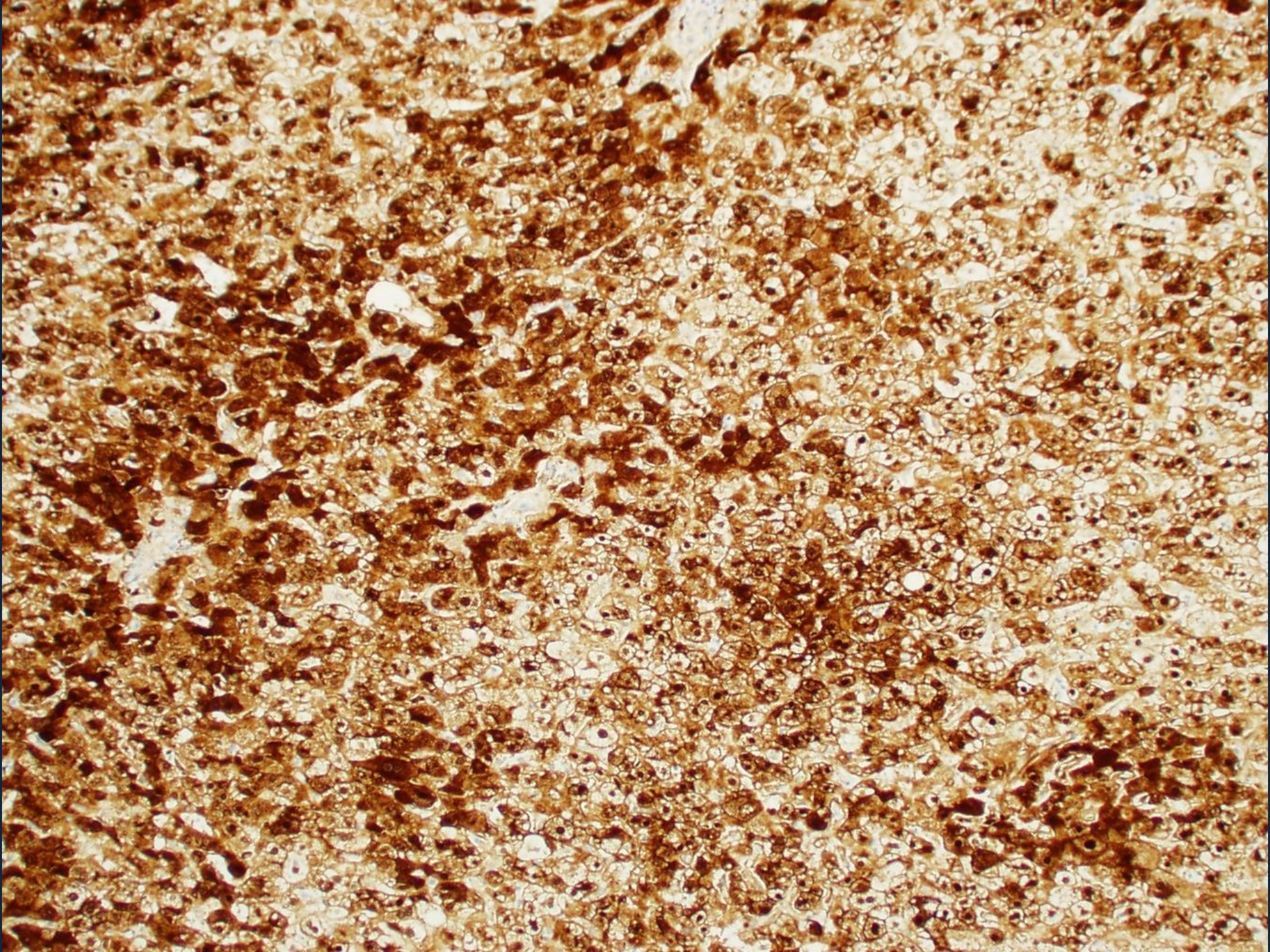
62/F, 6 cm liver mass

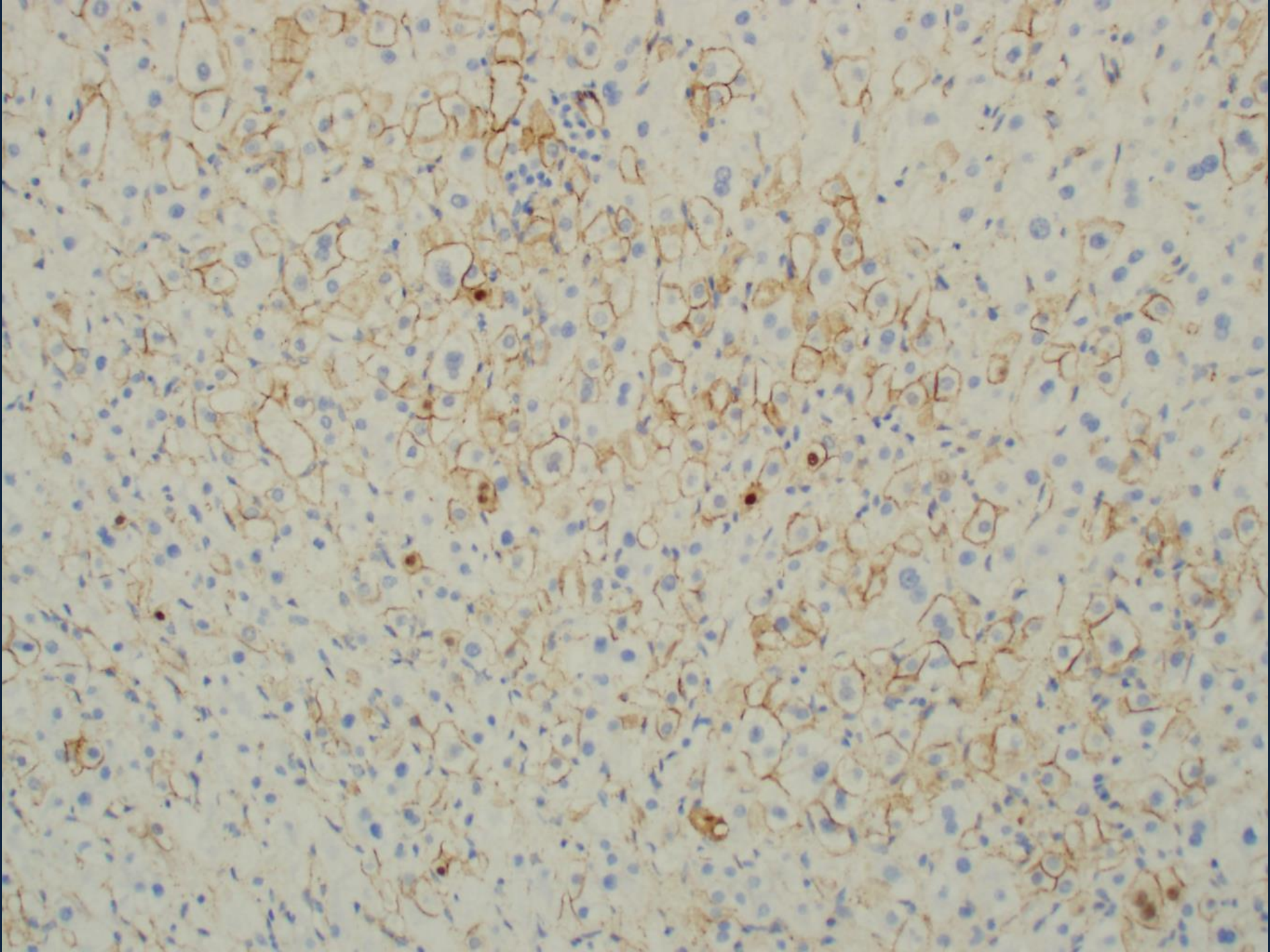


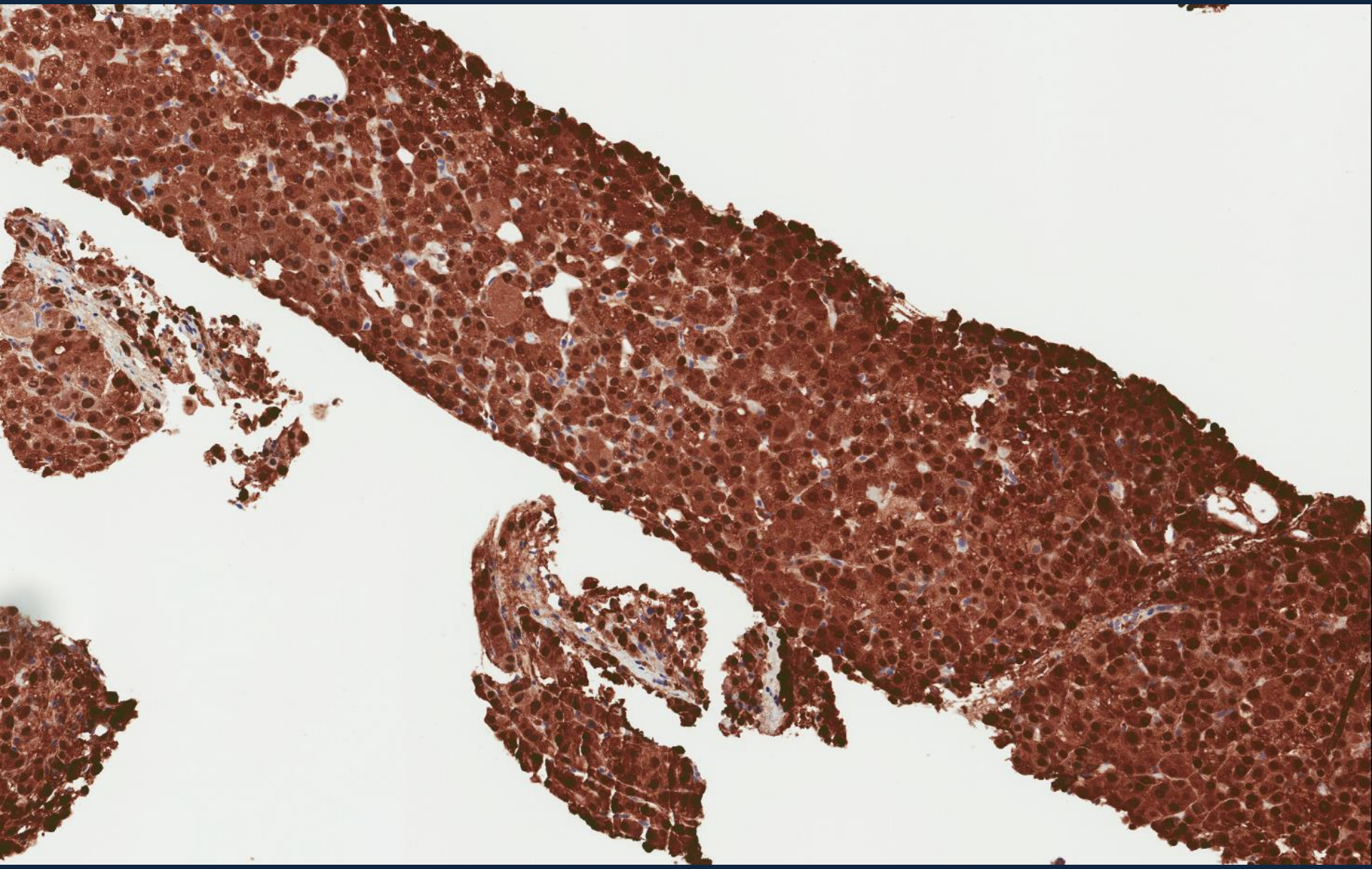
Nuclear atypia, no architectural changes

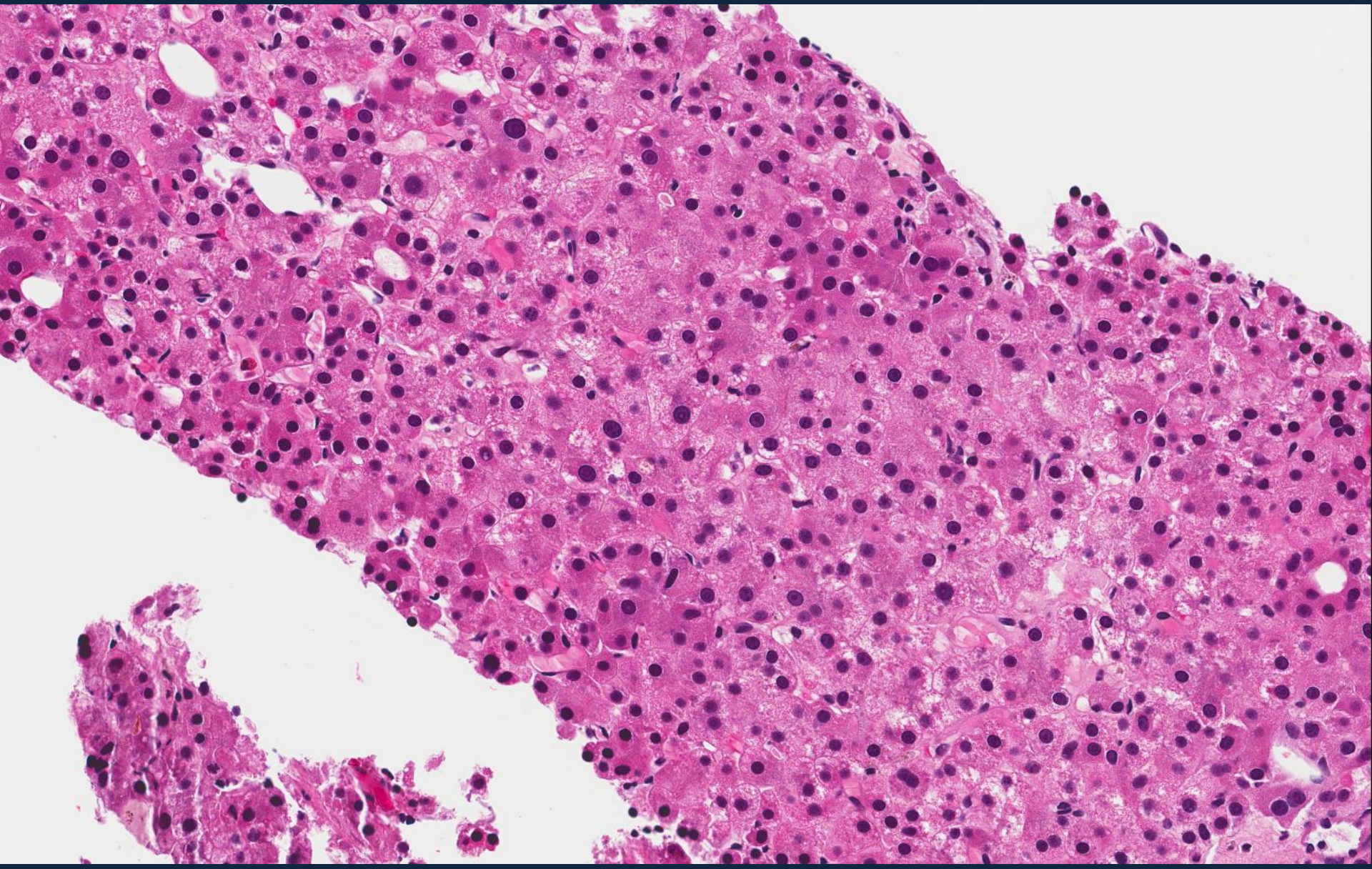


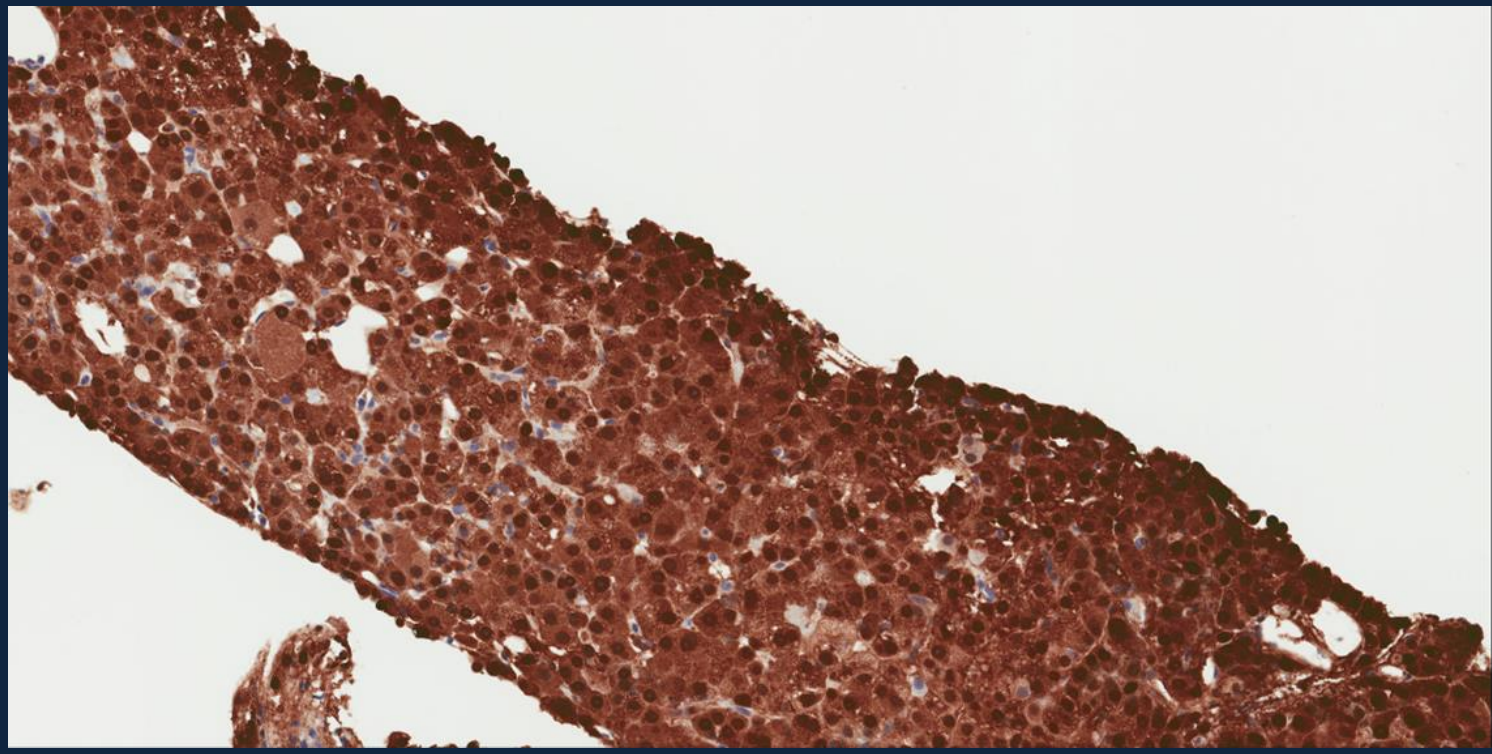


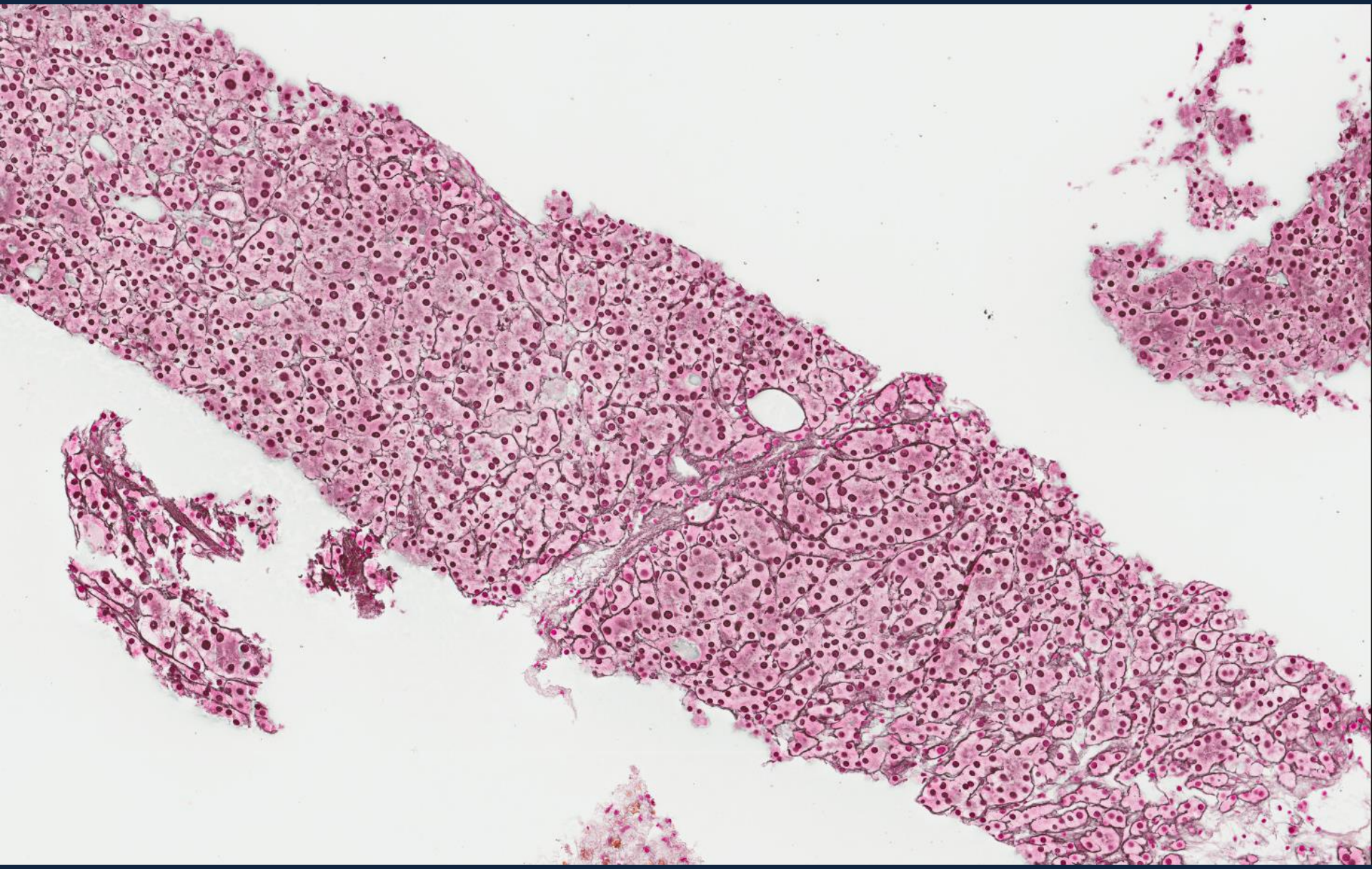




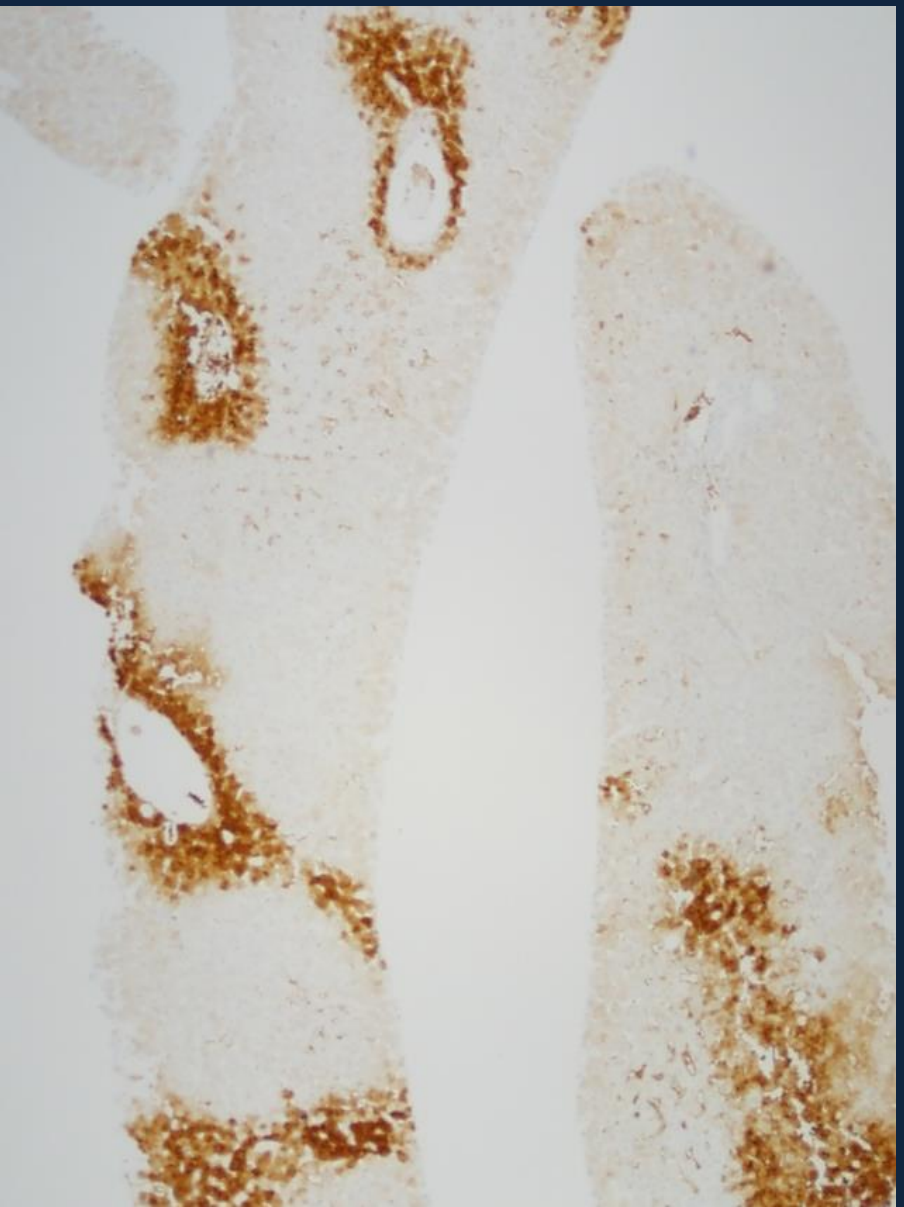




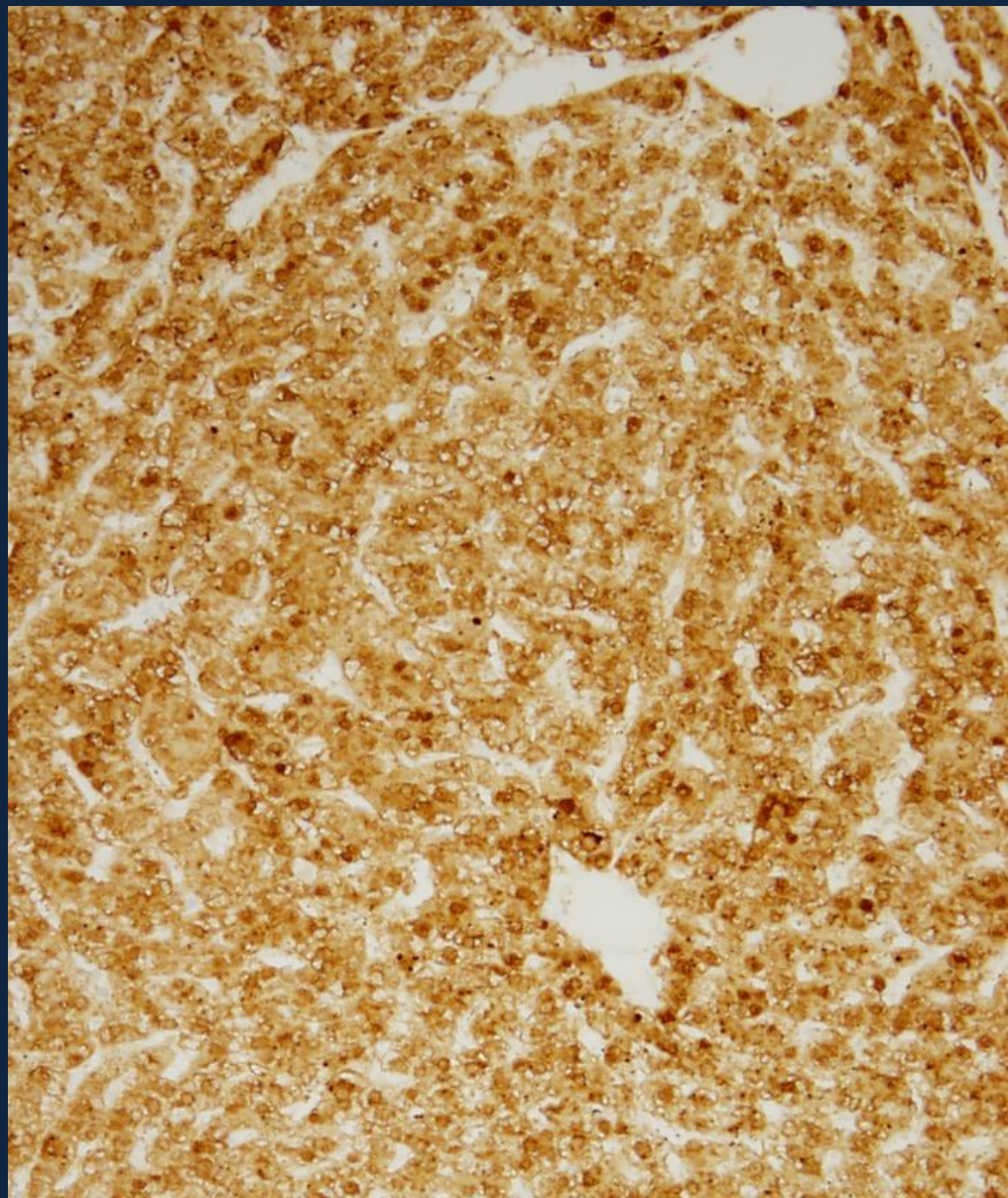


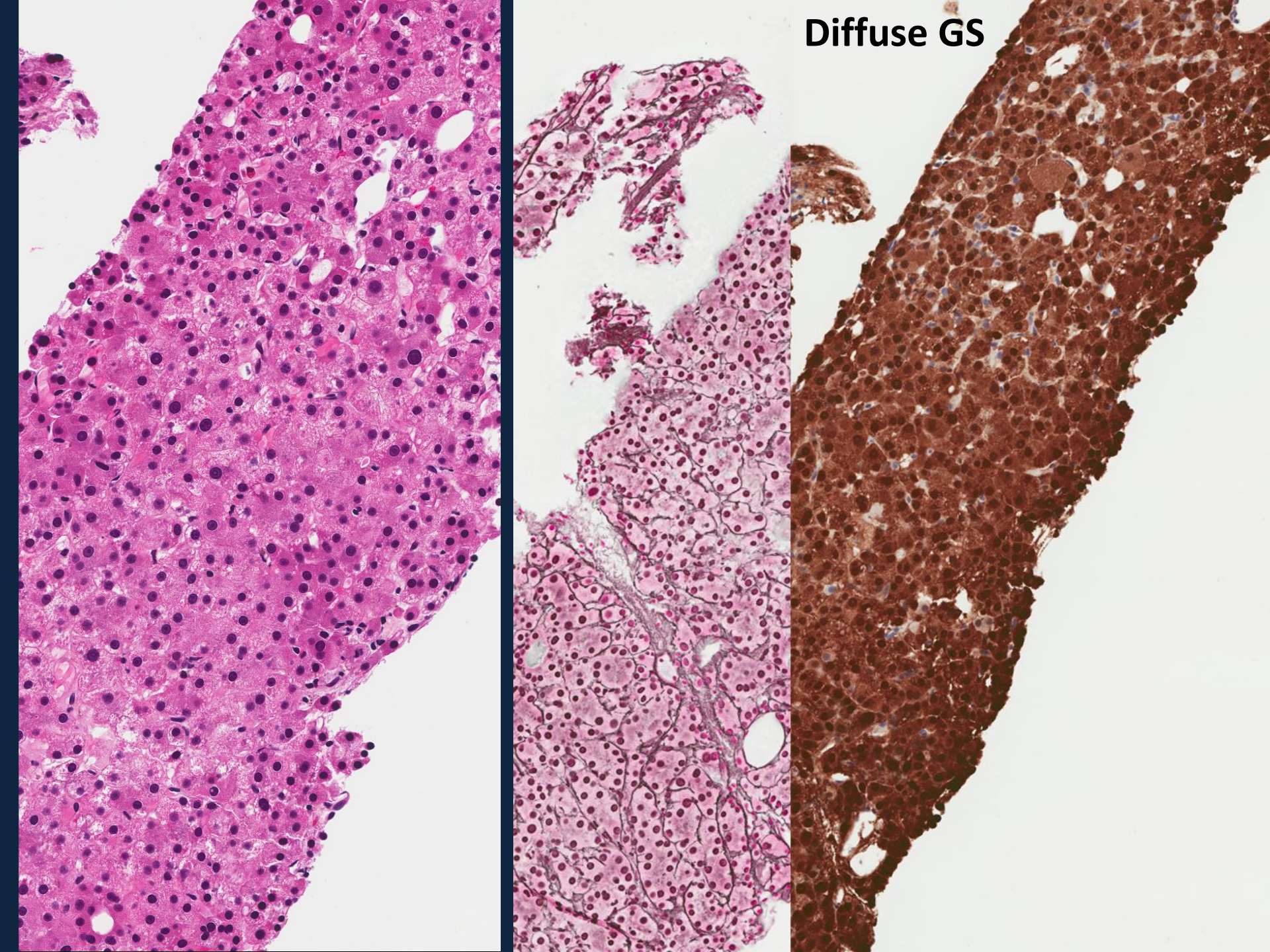


Normal liver: perivenular glutamine synthetase (GS)



β-catenin-activation: diffuse GS




Diffuse GS